Mannitol dry powder for inhalation for the treatment of cystic fibrosis

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Contributions of authors
Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment, critiqued the manufacturer's economic evaluation and contributed to the writing of the report. Nigel Armstrong acted as health economist on this assessment, critiqued the manufacturer's economic evaluation and contributed to the writing of the report. Kate Misso and Alexander Allen critiqued the search methods in the submission and contributed to the writing of the report. Nathan Manning acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Doreen Allen Tushabe acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Johan L. Severens acted as health economic project lead, critiqued the manufacturer's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the manufacturer's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse Event
AiC	Academic in Confidence
Bcc	Burkholderia cepacia complex
BSC	Best Supportive Care
CAS	Chemical Abstracts Service
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFTR	CF Transmembrane Conductance Regulator
CI	Confidence interval
CiC	Commercial in Confidence
CR	Clarification Response
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CVS	Chorionic Villus Sampling
DARE	Database of Abstracts of Reviews of Effects
DIOS	Distal Intestinal Obstruction Syndrome
DMARDS	Disease Modifying Anti-Rheumatic Drug
DSU	Decision Support Unit
EMA	European Medicines Agency
EQ-5D	European Quality of Life 5 Dimensions
ERG	Evidence Review Group
FEV1	Forced expiratory volume in one second
HS	Hypertonic Saline
HTA	Health Technology Assessment
HRQL	Health Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
KSR	Kleijnen Systematic Reviews
MD	Mean Difference
MMRM	Mixed model repeated measures
MRSA	Meticillin-resistant Staphylococcus aureus
MS	Manufacturer Submission
MTC	Mixed Treatment Comparison
MTX	Methotrexate
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NMB	Net monetary benefits
NR	Not reported
NSAIDS	Non Steroidal Anti-Inflammatory Drug
Pa	Pseudomonas aeruginosa
PAS	Patient Access Scheme
PDPE	Protocol defined Pulmonary Exacerbations
PRESS	Peer Review of Electronic Search Strategies
PSA	Probabilistic Sensitivity Analysis
PSS	Personal and Social Services
QALY	Quality Adjusted Life Years
QOL	Quality of Life
RCT	Randomised Controlled Trial
RR	Risk Ratio
SE	Standard Error
SF-36	Short Form 36
SAE	Serious Adverse Events
STA	Single Technology Assessment
TAG	Technology Appraisal Guidance
TAR	Technology Assessment Report
WHO	World Health Organisation

Contents

1 SUMMARY

1.1 Scope of the manufacturer submission

The NICE scope for this appraisal was to assess the clinical effectiveness and cost effectiveness of mannitol dry powder for inhalation, alone or in combination with rhDNase, compared with inhaled mucolytics (rhDNase), nebulised hypertonic saline, or best supportive care in people with cystic fibrosis.

However, according to the industry submission the expected license indication for mannitol is for: *"treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to rhDNase, and in adults ineligible, intolerant, or inadequately responsive to rhDNase"*.

This means that the population, intervention and comparators have changed from the original scope. After discussion with NICE it was agreed that there are now two distinct interventions for two separate populations: (1) Mannitol in combination with rhDNase for adults with cystic fibrosis, and (2) Mannitol alone for adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase. Regarding comparators, it was agreed that rhDNase is no longer a relevant comparator.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The industry submission provides evidence from two RCTs comparing mannitol 400mg with mannitol 50mg over 26 weeks in people with CF, aged >= 6 years (studies 301 and 302). According to the manufacturer "*the control arm in both studies was the equivalent of best standard of care on the grounds that mannitol 50 mg should not have any effect in these patients"*. Data from both trials are publicly available as conference abstracts only. Data from these two trials would allow for a comparison of mannitol with best supportive care in both populations (adult rhDNase users and adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase). However, in the MS only lung function is reported for one of the relevant populations for this appraisal: adult rhDNase users. In response to the clarification letter, the ERG received data for both populations, adult rhDNase users and adults who are ineligible, intolerant, or inadequately responsive to rhDNase, for change in FEV1 (graphs only) and exacerbations. No other data were provided, despite our request for all relevant data for the relevant populations. Results show that in adult rhDNase users, there are no significant differences in exacerbations between mannitol and best supportive care (incidence: RR=1.00 (95% CI: 0.61, 1.66); rate ratio per year: 1.14 (95% CI: 0.75, 1.73)); but mannitol leads to a significant improvement in change in FEV1 (MD=91.77 (95% CI: 30.85, 152.69)) when compared with best supportive care. In adults who are ineligible, intolerant or inadequately responsive to rhDNase, there are also no significant differences in exacerbations between mannitol and best supportive care (incidence: RR=0.44 (95% CI: 0.18, 1.10); rate ratio per year: 0.50 (95% CI: 0.18, 1.40)); but mannitol leads to a significant improvement in change in FEV1 (MD=162.32 (95% CI: 51.77, 272.87)) when compared with best supportive care.

In order to compare mannitol with hypertonic saline, the manufacturer performed a feasibility study to determine whether mannitol could be compared with hypertonic saline via indirect comparison. The manufacturer concluded that: "Based on this feasibility study, an indirect comparison of Bronchitol and hypertonic saline was not felt to be an appropriate analysis in this situation."

The ERG agrees with most objections of the manufacturer regarding heterogeneity between studies. Nevertheless, given the fact that hypertonic saline was mentioned explicitly in the NICE scope, the ERG would like to present the results of an indirect comparison based on current best available evidence. However, it should also be stressed that some data had to be guessed from graphs, making the analyses even more unreliable.

Results of the indirect comparison showed that there is no statistically significant difference between mannitol and hypertonic saline in terms of change in FEV1 in adult rhDNase users (MD = 23.77 (-64.95, 112.49)). In adults who are ineligible, intolerant, or inadequately responsive to rhDNase, there is no significant difference between mannitol and hypertonic saline in terms of change in FEV1 (MD = 94.32 (-33.67, 222.31)). In terms of exacerbations, hypertonic saline seems superior in adult rhDNase users; although, an indirect comparison is not possible because different outcomes are reported for the different studies.

1.3 Summary of cost effectiveness evidence submitted by the manufacturer

Based on searching published literature in PubMed and CRD databases the manufaturer identified 10 cost effectiveness studies, however none of these carry out cost effectiveness studies on mannitol. Therefore no specific conclusions from the economic review were provided in the MS.

The manufacturer provided a *de novo* individual patient simulation model based on a Markov health state transition model, using a life expectancy time horizon. This model was run for two separate populations: adult rhDNase-users comparing mannitol+rhDNase (with rhDnase+best supportive care (BSC) in case of inadequate lung function respons (FEV1 % predicted) after 6 weeks) vs. rhDNase+BSC and adults ineligible, intolerant, or inadequately responsive to rhDNase comparing mannitol (with BSC in case of non-respons) vs. BSC. Disease progression is captured by the individual patients decline in FEV1 % predicted. Acute worsening of lung function is captured as pulmonary exacerbation leading to hospitalization. The rate of pulmonary exacerbations depends upon treatment, the patient's age, and the history of exacerbations in the previous year. FEV1 % predicted at 26 weeks is predicted using a regression model, including treatment group, BMI at baseline, FEV1 % predicted at 6 weeks, respiratory symptoms and responder/non-responder as covariates. For all subsequent cycles, FEV1 % predicted declines with age and exacerbations. Probability to die relates to either CF (based on lung function, age, exacerbation, and Bcc infection), lung transplantation, or to unrelated cause. Average changes in utility from average baseline utility values measured in one of the two included trials (study 301 and 302) determined the utility value of each Markov state. Exacerbations, being eligible for lung transplant and receiving a lung transplant had impact expressed in utility change, all derived from the literature. Resource use was derived from both included trials to value Markov state costs for the treatment options. Exacerbation costs were also derived from the trial data, whereas costs of lung transplant and the costs post lung transplant were taken from literature. For the first 26 weeks, individual patient level data from the two included clinical studies were used. From here the model uses Australian observational data and literature. The various outcomes as reported in the clinical effectiveness section of the MS were not used in the economic model; for the model separate analyses were performed.

The base-case cost-effectiveness results of the manufacturer's submission were originally for the rhDNase users (mannitol + rhDNase versus BSC + rhDNase) £47,095/QALY and for the rhDNase unsuitable patients (mannitol vs BSC) £41,074/QALY.

1.4 ERG commentary on the robustness of evidence submitted by the manufacturer

1.4.1 Strengths

The industry submission is based on two high quality randomised controlled trials (DPM-CF-301 and DPM-CF-302) with a total of 600 participants divided over two treatment arms in the two trials. In addition, a systematic review was undertaken with the aim to perform an indirect comparison between mannitol and hypertonic saline.

The manufacturers search strategies were clearly documented and for the most part contained well defined PICO (population, intervention, comparator, outcome) components. Appropriate truncation and line combinations were applied throughout. Useful additional searches of trials registers, conference abstracts and the Pharmaxis in-house database were undertaken.

The two trials were well designed and thus provided a potentially strong evidence base for an economic evaluation of mannitol in the management of cystic fibrosis.

Regarding the cost-effectiveness analyses as submitted by the manufacturer, a strength is the fact that the analyses are based on a *de novo* model taking into account the specific features of cystic fibrosis. The use of an individual patient simulation model makes it possible to take variability in patient characteristics into account explicitly. The CEA model was constructed according to the NICE reference case with utility and long term cost estimates.

1.4.2 Weaknesses

The main weaknesses of the industry submission relate to the changes to the scope due to the expected licence indication. This means that data can only be used for adult patients (N=341 from the two trials); and data should be analysed separately for adult rhDNase users (n=207) and adult CF patients for whom rhDNase is unsuitable (n=65). In addition, very few outcomes have been reported specifically for the two populations of interest for this appraisal.

A second major weakness of the industry submission is the fact that a comparison with the main active comparator, hypertonic saline, is missing, which affects the ability to assess both effectiveness and cost effectiveness.

The search strategies in the MS included very limited synonyms for cystic fibrosis and mannitol which could have affected recall of relevant references. The manufacturer failed to search two of the required databases, Embase and EconLIT, for the cost-effectiveness, measurement and valuation of health effects, and resource identification sections. Many searches incorporated an unnecessary English language limit which might have introduced language bias into the search results. No specific searches for adverse events were undertaken and the clinical effectiveness search used for this purpose was not appropriate due to its RCT filter. This filter, along with those used in the cost effectiveness and HRQL searches, was basic and

was shown to reduce retrieval heavily when compared to objectively derived filters used in the ERG searches.

A major weakness of the cost-effectiveness analyses was the selection of data: data from all adult patients was used to inform both the cost-effectiveness of mannitol versus control (patients ineligible, intolerant, or inadequately responsive to rhDNase treatment) and of mannitol plus rhDNase versus BSC plus rhDNase (rhDNase users). Although this question for clarification was partly solved in the manufacturers' response, the revised baseline analysis and the uncertainty analysis were based on this omission, thus using data from the wrong population. Furthermore, treatment dependent data were used for valuing health states. Besides, the effectiveness outcomes used in the clinical effectiveness section of the MS have little relevance for the economic model and/or were not used in the model.

The Markov states and transitions defined in the model describe more the clinical studies with mannitol than the natural disease course of cystic fibrosis. In general, relative health states (such as improved respiratory symptoms) should be avoided, although the individual patient simulation deals with this difficulty adequately. The validation of the model (especially the extrapolation beyond the trial time horizon of 26 weeks) was limited. However, the ERG believes that remaining imperfections will have limited impact on the major conclusion given the fact that sensitivity analyses indicate robustness of the findings.

1.4.3 Areas of uncertainty

The main areas of uncertainty relate to the outcomes not reported for the relevant populations: mortality, respiratory symptoms, exercise tolerance, adverse events and quality of life.

In addition, the clinical effectiveness of mannitol compared to best supportive care is uncertain in adult CF patients for whom rhDNase is unsuitable, with only 65 respondents in the two treatment arms from two different trials.

There is insufficient data for a reliable comparison between mannitol and hypertonic saline.

Regarding cost-effectiveness, it was assumed that the initial gain in FEV1 % predicted would be maintained over lifetime for which there is only limited evidence from one of the trials. Additionally, it was assumed that the probabilities of improving respiratory symptoms in the next cycle and of moving from improved to not improved would stay the same over lifetime, for which no evidence was available. It was shown by the ERG that varying this assumption has a major impact on the cost-effectiveness estimate.

For the calculation of the effect of treatment on the rate of exacerbations, the PDPE (Protocol Defined Pulmonary Exacerbation) rates have been used. This implies that the rate ratio of PDPE in mannitol versus control may be used as a proxy for the rate ratio of having a severe exacerbation. It is difficult to assess whether such proxy will be an over- or underestimation; however, for the time being the ERG considers this to be best available evidence.

1.5 Key Issues

For the comparison with BSC, we only have data for lung function and exacerbations. No data was provided for other outcomes, such as: quality of life and adverse events. Lung function seems to favour mannitol over BSC; while there was no statistically significant difference between mannitol and BSC for exacerbations

For the comparison with hypertonic saline, no direct evidence was available. In addition an indirect comparison was not possible, partly because of heterogeneity between studies, but also partly because data was not provided by the manufacturer. The ERG thinks more could have been done here. The available evidence seems to suggest that lung function favours mannitol, while exacerbations seem to favour hypertonic saline in rhDNase users.

The manufacturer argues that hypertonic saline is not a relevant comparator for this appraisal, which directly contradicts the NICE scope. This should be resolved.

The base-case cost-effectiveness results of the manufacturer's submission were originally for the rhDNase users (mannitol + rhDNase versus BSC + rhDNase) £47,095/QALY and for the rhDNase unsuitable patients (mannitol vs BSC) £41,074/QALY. Further analysis by the ERG suggests that, when population specific data and some alternative assumptions are used, the ICER in the rhDNase users group increases to £82,508/QALY whereas the ICER in the thDNase unsuitable group decreases to £29,883/QALY.

The PSA performed by the ERG showed that for the assessment of mannitol in rhDNase users, the probability that the ICER will below a threshold of £30,000 QALYs per year is zero. In rhDNase unsuitable patients, the probability that the ICER is below £20,000 and £30,000 is 5% and 50%, respectively. Scenario analyses varying the exacerbation rate in the control group and running subgroup analyses according to baseline FEV1 % predicted did not impact on the conclusions about the cost-effectiveness of mannitol for both populations. Relaxing the assumption that mannitol efficacy is life-long has a major negative impact on the cost-effectiveness estimate.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem.

Does the ERG believe that the manufacturer's description of the underlying health problem is appropriate and relevant to the decision problem under consideration?

The MS defines Cystic Fibrosis (CF) in a rather 'pessimistic' way focussing on predominantly disease complications. The ERG group believes the section below provides a more balanced approach to the definition of CF.

Cystic Fibrosis is an inherited recessive genetic disorder that affects primarily the lungs. The prevalence of CF is dominant in the Caucasian population. Around 8000 of the UK population have CF, of which 4500 are children. At least 5 babies are born with CF and 2 CF deaths are recorded each week. In the United Kingdom, 1 in 25 people are CF carriers while 1 in 2500 people has CF.[1] CF is caused by a faulty gene called CF Transmembrane Conductance Regulator (CFTR), which helps regulate salt and water movement across the epithelial cells.[2] The disease manifests in many organs, in particular, the upper and lower airways, bowel, pancreas and reproductive tracts. Symptoms appear throughout life and with considerable overlap and variability in both symptoms and timing of symptoms. Nonetheless, lung disease is the major cause of morbidity and mortality in CF.

Viral infections among infants with CF are not more frequent than healthy infants but are more likely to be symptomatic.[3] Bacterial infections manifest early in life for CF patients, typically followed by permanent colonisation of the airways. A range of bacteria may appear during this period, but *Pseudomonas aeruginosa* quickly becomes predominant[4] and will eventually lead to the formation of a biofilm in the lungs. This development indicates a significant increase in the decline of pulmonary function as it exacerbates the inflammatory response and tissue damage. Over time mild emphysema may develop. Bacterial infections continue and exacerbations may require treatment as eradication of infection is highly unlikely. With time airway invaders may be supplanted by more resistant organisms: meticillin-resistant *Staphylococcus aureus* (MRSA), yeast, and fungus are common.[5]

There is no cure for CF and life expectancy is hard to predict because the disease affects individuals differently. Recent decades have seen significant improvements in the outlook for patients with CF, due earlier diagnosis of CF through screening. The main factors influencing the prognosis of a CF patient are: treatment compliance, treatment efficacy and the accessibility to healthcare. Predictions made in the mid-1990s that life expectancy would double from 20 to 40 years are now coming to fruition.[6] For babies born in the 21st century the predicted median survival is more than 50 years.[7] As survival rates continue to increase, the disease is shifting from a digestive and lung disease of children, to a complex multi-system disease which extends into adulthood.[5, 8] With the increased life expectancy, CF patients may develop various disease related complications such as: haemoptysis, respiratory and cardiac failure, chronic liver disease, chronic Distal Intestinal Obstruction Syndrome (DIOS), Allergic Bronchopulmonary Aspergillosis (ABPA), nasal polyposis, osteoporosis, male infertility, inflammatory arthritis, oesophageal reflux, oesophagitis, diabetes mellitus as well as psychological and behavioural problems.[9]

2.2 Critique of manufacturer's overview of current service provision

Does the ERG believe that the manufacturer's overview of current service provision is appropriate and relevant to the decision problem under consideration?

Cystic Fibrosis Screening aims at reducing birth prevalence, improving diagnosis in addition to providing information on appropriate management of the condition. Genetic screening is associated with the potential of reducing the burden of CF, in such a way that, from the information about gene frequency of various CFTR mutations, it is more likely to foresee the inequitable power of genetic screening. Antenatal screening in the UK is highly recommended and is also acceptable to the majority pregnant women and their partners, with very minimal psychological problems experienced.[11] In neonatal screening alone, the detection rate is thought to be at an average of 90%, and in combination to genetic screening, the detection rate is estimated at 97%. However, what is not clear is whether early diagnosis of CF through screening will improve the long term prognosis of the condition. The cost per affected birth detected by antenatal screening is projected at a value of at least £143,000.[12] From a cost-benefit analysis, averted treatment costs are estimated to be much higher than the cost of screening itself. During the financial year, 1989–90, in an adult UK CF centre, the average cost of care per patient was £8200; in 1996, the annual average cost of treatment for children was £10,567, ranging from £5310 in those aged 0-4, to £12,945 in patients aged 15 years and above, respectively.[11, 13, 14]

CF individuals often undergo rigorous treatment regimens daily. The cost of treating CF is dependent on the treatment and the CF centre. For example, based on 2000 and 2001 data from a UK adult CF centre: Wythenshawe Hospital in Manchester, on average CF Patients who had at least 60% of antibiotic courses at home over 1 year had a mean cost of £13,528, in comparison to £22.609 for those who had at least 60 % of courses in the hospital, and a mean total cost of £19,927 for those who had both hospital and home care ($p=0.0001$). The figures are assumed to be much lower with the use of Hypertonic Saline based on a concentration of 6%-7%.[15] CF treatment is often customised. Mortality in CF is often associated with airway infections thus standard care is directed at detecting and eradicating such infections. Basic standard care involves use of various medication and therapies such as bronchodilators, antibiotics, steroids, rhDNase, hypertonic saline, Physiotherapy. Long term use of hypertonic saline in CF patients is thought to be clinically effective mucociliary clearance.[16, 17] MS pg. 21 suggests that from a survey by Pharmaxis, 80% of CF UK centres use hypertonic saline.

Currently, there is no NICE guideline on the treatment options for CF. The CF trust developed a guideline on the standard care of CF in Children and Adults in UK and recommends full or shared specialist care for all CF patients. In the UK, paediatric CF centres are well established and advanced but adult CF centres are non-existent, and so is the expertise to treat adults CF patients. Complexity in care is evident with the increased life expectancy. Variations in treatment options are evident based on patient needs but improvements and new developments are continuously progressing. Therefore, with CF associated complications, adult specialist centres are key priority in the UK to meet patient demands.[9]

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

To what extent does the clinical evidence submitted by the manufacturer match the patient population described in the final scope? Where there is a mismatch, provide further details. Does the clinical evidence submitted by the manufacturer reflect the characteristics of the patient population in England and Wales eligible for treatment? If not, provide further comment.

The eligible population for mannitol based on the NICE scope is "*people with Cystic Fibrosis"*. In section 4, the industry submission clearly defines the population as *"Adults (18 years and above) with Cystic Fibrosis"*. This is different from the scope due to the fact that the current Bronchitol label is restricted to adults only and the rationale for this is provided by the MS. This is further supplemented by authorisation from NICE about the licence indication being for adults only; therefore, the description of the population in the MS is considered appropriate.

From the MS, two population categories are evident and these include:

- Mannitol as add-on therapy for rhDNase users
- Mannitol alone for adult CF patients who are ineligible, intolerant or inadequately responsive to rhDNase

It should be noted that in the original MS, pooled analyses on all rhDNase users and rhDNase non-users in the overall population were presented; in addition results were reported for adult CF patients. However, results were not reported separately for adult rhDNase users and adult rhDNase non-users. In the response to the clarification letter, the manufacturer provided data for adult rhDNase users and adult CF patients who are ineligible, intolerant or inadequately responsive to rhDNase separately. However, only data for lung function and exacerbations were provided for these populations.

3.2 Intervention

Does the intervention described in the MS match the intervention described in the final scope? What is the technology and what is its relevant or proposed marketing authorisation/ CE mark?

The submission describes the intervention as 'mannitol dry powder for inhalation' and provides information on the current status of the marketing authorisation in section A (MS, chapter 1.4, page 14-15). There is no mismatch with the NICE scope, however, the marketing authorisation is sought for indication of Bronchitol as a treatment for cystic fibrosis in adults aged 18 years and above as an add-on therapy for rhDNase, and as mono-therapy in patients ineligible, intolerant, or inadequately responsive to rhDNase. The recommended dosage is 400mg (10 capsules) twice daily for a life time. The time frame considered is appropriate for a chronic condition like CF. Bronchitol does not currently have a UK marketing authorisation for the treatment of cystic fibrosis.

3.3 Comparators

Do the comparators described in the MS match the comparators described in the final scope? If not, provide further details. Where evidence is limited or not available for relevant comparators has the manufacturer asked an unbiased clinical panel, or carried out its own survey, and do the views elicited agree with what the clinical advisors to the ERG advocate?

There was a mismatch between the scope and the decision problem in the MS regarding the comparators. The scope states comparators to be: inhaled mucolytics (rhDNase), nebulised hypertonic saline, and best supportive care which the MS completely acknowledges in the statement of the decision problem (MS, chapter 4, page 25). However, the main comparators for mannitol in the submission are: best supportive care, and best supportive care with rhDNase. Current best supportive care for the management of CF includes use of bronchodilators, steroids, physiotherapy, inhaled antibiotics, anti-inflammatory agents and vitamin supplements.

No data is provided in the MS for the comparisons with hypertonic saline and rhDNase. The ERG agrees that rhDNase can be ignored as a comparator as all adult CF patients using rhDNase will receive mannitol in combination with rhDNase; or alternatively, mannitol alone will be used in CF patients who are ineligible, intolerant or inadequately responsive to rhDNase. However, a comparison with hypertonic saline is still relevant and it is specifically mentioned in the NICE scope.

According to information provided by the manufacturer in their response to the clarification letter, "the main argument for not comparing mannitol to hypertonic saline was not the absence of a common control arm, but rather to significant differences in the design and target population between the mannitol and the hypertonic saline studies." (Response to clarification letter, page 13-14). The ERG agrees that there is heterogeneity between studies; especially regarding baseline antibiotics use and baseline FEV1 (see also section 4.2.7). However, given the fact that hypertonic saline is explicitly mentioned in the NICE scope it is important to provide an indirect comparison based on the best available evidence. Nevertheless, heterogeneity between studies should be taken into account when interpreting the results.

3.4 Outcomes

Do the outcomes in the MS match the outcomes described in the final scope? If not, provide further details. Consider clinical effectiveness, adverse events, quality of life and health economic outcomes and a discussion of appropriate mechanisms for measuring these outcomes. Is the focus of the submission on appropriate outcomes or has it been limited to non-ideal outcomes?

In section 4 of the MS, there is no mismatch between the outcomes listed in the submission and those listed in the scope. All outcomes listed in the scope will also be included in the decision problem addressed in the submission according to the MS. Nevertheless, data on mortality are not assessed in any of the studies included in the submission; and data on respiratory symptoms, exercise tolerance, adverse events and health-related quality of life are not reported for the relevant populations in this appraisal.

Therefore, data are missing for 5 out of 7 outcomes specified in the NICE scope.

3.5 Other relevant factors

For example: Does the MS include a section on equity considerations? Is there an ongoing Patient Access Scheme application?

According to the manufacturer, there are two issues that may prevent equal access to the technology (MS, chapter 3.1.2, page 23):

- Once considered a childhood disease, cystic fibrosis is now also a disease of adults. Increased longevity has resulted in the aging of the cystic fibrosis population. Current label of Bronchitol is restricted to adults. In the clinical trials patients 6 years and older were included however as described in section 1.4, the determination of the benefit/risk in the 6-17 year age group is problematic due to the apparent control effect, despite there being a meaningful improvement from baseline at 400mg. The population of children studied continue to have an important unmet need, and Pharmaxis intends to apply for an indication in younger patients in due course.

- It is possible that patients with physical disabilities associated with impaired manual dexterity may find it difficult to load capsules into the inhaler, and might not be able to use Bronchitol without assistance.

As the current license application only includes adults, the first consideration is not relevant for this appraisal. Regarding the second consideration the manufacturer states that “there were no patients with physical disabilities included in the clinical trials”.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods used by the manufacturer to systematically review clinical effectiveness evidence

The NICE scope mentions the following treatments used alone or in combination with each other as comparators:

- Inhaled mucolytics: rhDNase
- nebulised hypertonic saline
- best supportive care (which may include a wide range of inhaled and oral active treatments)

For the comparison with BSC, the MS reports evidence from two RCTs comparing mannitol 400mg with mannitol 50mg over 26 weeks in people with CF, aged >= 6 years (studies 301 and 302). Data from both trials are publicly available as conference abstracts only.

For the comparison with hypertonic saline the MS mentions a feasibility study to determine whether mannitol could be compared with hypertonic saline via indirect comparison. Based on this feasibility study, an indirect comparison of mannitol and hypertonic saline was not felt to be an appropriate analysis.

The comparison with rhDNase was not mentioned in the MS. This is because according to the latest information regarding the expected license indication, mannitol will be either used as an add-on therapy to rhDNase or as monothereapy in patients ineligible, intolerant or inadequately responsive to rhDNase. (page 16 MS)

4.1.1 State objective of systematic review. Provide description of manufacturers search strategy and comment on whether the search strategy was appropriate. If the manufacturer did not perform a systematic review, was this appropriate?

List databases and other sources of information including unpublished sources, describe any restrictions.

An evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), developed by McGowan,[18] was adapted to serve as a template for this critique. The submission was checked against the Single Technology Appraisal (STA) specification for manufacturer/sponsor submission of evidence,[19] to show that retrieval could be improved. The ERG created a number of comparison search strategies and re-ran many of those created by the manufacturer. The ERG search strategies are presented in Appendix 2. In all but one case, the ERG was not able to screen search results due to time constraints, and therefore can only show the numerical differences in the numbers of references retrieved between manufacturer and ERG searches without a definitive indication that relevant studies were missed.

4.1.1.1 Clinical effectiveness

Page 28 of the manufacturer's statement,[20] states that search was carried out in two "phases", phase one included the entire cystic fibrosis (CF) population, and phase two only the adults. However since both first and second phase searches were identical and were carried out on the same day, the ERG critiqued them as one.

The databases searched (page 211) were in line with NICE's guidance; Medline, Medline In-Process, Embase, and Cochrane Library, with additional searches using ClinicalTrials.gov, the NICE website and a search of Pharmaxis' data using their EMA license application for Bronchitol. The providers for each database were listed, as were the dates of searching. Limited details of the date span of searches were reported. The start date for each database was accurate but the end date was not for the following:

- Medline: the specific month and week was not reported, for example OvidSP Medline 1948 to March Week 4 2011.
- Medline In-Process: The dates of the last update, for example, OvidSP Medline In-Process & Other Non-Indexed Citations March 30, 2011.
- Embase: the year and week was not reported, for example OvidSP Embase 1980 to 2011 Week 12.
- Cochrane Database of Systematic Reviews (CDSR): the year and issue, for example Issue 3 of 12, Mar 2011.
- Cochrane Central Register of Controlled Clinical Trials (CENTRAL): the year and issue, for example Issue 1 of 4, Jan 2011.

The strategies were clearly structured into population and intervention facets with the addition of a study design filter, when supported by the database. While fundamentally sound in construction, sensitivity would have been improved by the inclusion of synonyms for mannitol and CF. The ERG identified several relevant synonyms for the population and intervention, including subject headings in Medline and Embase. By combining truncation and a wildcard in mannitol to create the search term "mann?t$" (valid in Medline and Embase), many relevant synonyms would have been retrieved without impacting on specificity. The Chemical Abstracts Service (CAS) registry number for mannitol would also have been a useful addition to the strategy.

The major criticism of this search was the use of an unreferenced randomised controlled trials (RCT) filter in the Medline, Medline In-Process and Embase searches. There were two reasons why the ERG felt this was problematic. Firstly, the number of references retrieved, without the inclusion of an RCT, could easily be screened by a reviewer (n=150 in Embase, n=77 in Medline and n=2 in Medline In-Process). The second reason was it would be preferable to incorporate an objectively derived RCT filter.[21] A selection of objectively derived study design filters/hedges can be easily identified for both OvidSP Medline and OvidSP Embase, by using the ISSG Search Filter Resource.[22]

The ERG could not fully reproduce the manufacturer searches, as the strategies in the MS (pages 214-215) did not report the field tags used for the Medline, Medline In-Process and Embase searches. The ERG assumed the basic keyword search function was employed, which applies the .mp tag by default. Comparison of the re-run manufacturer searches with those reported in the MS highlighted some inconsistencies in the results that could not be explained by changes in the database contents in the intervening period. The manufacturer reported 21,374 hits for the term "Bronchitol" in their Embase search whereas the ERG retrieved 20 hits. There were other smaller inconsistencies, such as the term "Mannitol" retrieving more hits in the manufacturer search than the more current ERG search. However this discrepancy may have been caused by field tags differences, for example .af. being used by the manufacturer but not reported. There was an error in the labelling in Table 111 (page 215) of a search undertaken in "Medline in Progress". This should have read Medline In-Process. There were also unnecessary apostrophes around cystic fibrosis in the Medline, Medline In-Process and Embase strategies.

The ERG created Medline and Embase search strategies using subject headings, synonyms and an objectively derived RCT filter. The results of this ERG search were compared with the updated manufacturer searches in the table below and highlighted the importance of the use of an objectively derived RCT filter. The manufacturer searches retrieved 251 references without the filter and only 23 with the RCT filter. The ERG searches retrieved 267 without an RCT filter and 54 with it. The ERG concluded that relevant studies might have been missed due to the basic filter employed by the manufacturer.

Table 1: Comparison of retrieval between manufacturer and ERG searches for clinical effectiveness

	References retrieved without RCT filter	References retrieved with RCT filter
Updated manufacturer searches		
Embase 1980-2011 wk 12	175	16
Medline 1948-2011, March, Week 4	76	7
ERG searches		
Embase 1980-2011 wk 12	183	41
Medline 1948-2011, March, Week 3	84	13

The Cochrane Library search had similar limitations as the Medline and Embase in terms of lack of synonyms and truncation. However the ERG's search, which included additional synonyms, retrieved only slightly more hits on CENTRAL (17 hits to 12) and no more hits on CDSR (3 reviews to 3 reviews) than updated searches using the manufacturers' strategy. The Cochrane search (page 215) appeared to be missing line 1 of the strategy. The ERG assumed this missing line should have read "Bronchitol", in the same way the other searches in this section did.

The MS stated that an additional search was carried out on ClinicalTrials.gov**.** The ERG created a new search for this resource using the synonyms from the previous clinical effectiveness searches and retrieved the same number of hits as the manufacturer (n=7). The MS did not include details of the search terms used to search the NICE website or the Pharmaxis in-house resources, therefore the ERG was unable to comment on these searches.

4.1.1.2 Indirect and mixed treatment comparisons

Page 220 of the MS stated the databases searched and these were in line with NICE's guidance. Medline, Medline In-Process, Embase and Cochrane Library were searched, supplemented by additional searches of Conference abstracts from European Cystic Fibrosis Conference (2008-2010), Conference abstracts from North American Cystic Fibrosis Conference (2008-2010) and ClinicalTrials.gov.

These searches were not documented in the MS; therefore the ERG requested further details as part of the clarification process.[23] The manufacturer's response to the clarification letter[24] documented search strategies for Medline, Embase and Cochrane Library. Several search strategies remained unreported, those for Medline In-Process, Conference abstracts from European Cystic Fibrosis Conference (2008-2010), Conference abstracts from North American Cystic Fibrosis Conference (2008-2010) and ClinicalTrials.gov. The ERG was unable to comment on searches without seeing the strategies.

The date searched was stated as 16.08.10 for all databases in the MS (page 220). The date spans of Medline and Embase were reported on page 33 of the Clarification Response (CR). Despite the ERG requesting this information in the clarification letter, the CR did not provide the issue numbers for the CDSR and CENTRAL searches. The date spans reported in the CR – 1980 to 2010 week 29 for Embase and 1950 to 2010 July week 3 for Medline - did not correlate with the search date. These date spans indicated a search carried out in late July and not mid-August.

The search itself was clearly translated from a research question into population, intervention and study type facets. Each of the facets contained both natural language and subject heading terms taking into account some synonyms and variants. While some subject headings could have been interpreted as overly broad, such as mucociliary clearance, hypertonic solution, surfactant, expectorant agent and surface-active agents, this extra sensitivity did not increase retrieval so much as to make screening unmanageable. The following subject headings were unnecessarily exploded as they are the narrowest terms in the MeSH hierarchy: cystic fibrosis, mucociliary clearance, sodium chloride and mannitol. While this is not a good technique, it does not affect the search results.

Boolean and proximity operators were used appropriately and correctly with truncation to create and combine the facets into a very adequate search. An extensive RCT filter was used.

Each of the search strategies in the CR incorporated a repeated line, so that Mannitol.mp. was searched twice (line 11 of the Embase strategy (CR page 34), line 11 of Medline strategy (CR page 34) and line 15 of the Cochrane search (CR page 35). The ERG assumed these repeat lines were reporting errors, as the numbers of references retrieved on these lines would suggest the MS actually searched for the term Bronchitol.

There was inconsistency between the MS and the CR. The MS stated that 919 studies were retrieved in total from the searches in all of the databases above, but according to the CR (pages 34 & 35) the Medline, Embase and Cochrane Library searches alone retrieved 922 studies.

The strategies were presented clearly enabling the ERG to replicate the searches. The ERG re-ran the manufacturer Medline, Embase and Cochrane Library strategies, limiting to studies post 2009 and removing the Mannitol facet. The resulting searches aimed to find relevant studies investigating

hypertonic saline for CF. These 152 results were downloaded into an Endnote Library and de-duplicated to leave 123 studies for reviewers to screen. The reviewers did not find any relevant studies.

4.1.1.3 Adverse events

The MS did not report searches for adverse events (AE), therefore the ERG assumed no systematic searching had been carried out. Instead the adverse events data was extracted from studies identified using the manufacturer's clinical effectiveness searches. The CRD guidance[21] recommends that if effectiveness searches have been limited by an RCT filter additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. It is recommended that further searches are carried out on the same resources as well as additional specialist resources. The manufacturer employed a very basic RCT filter but did not carry out further searches or use any specialist resources to find adverse events data. For this reason, the ERG was concerned that relevant AE data might not have been identified.

4.1.1.4 Cost effectiveness

The search concepts were stated as "cost effectiveness" combined with "cystic fibrosis". This appeared to be a revised approach, as the first search in appendix section 9.10.4 contained a mannitol facet as well. The original search retrieved 0 hits. At that point, the manufacturer expanded the search parameters by removing the mannitol facet. The ERG felt the alteration of search strategy should have been reported in the main report text as well as the appendix.

The manufacturer searched PubMed and the CRD databases. The PubMed search covered Medline and Medline In-Process, and the CRD databases encompassed NHS EED. The MS stated that Cochrane Collaboration was searched (page 114); no details of a search strategy were reported, but the MS states the search retrieved 2 hits. The ERG was unable to reproduce this search. Although the MS and CR reported several Embase search strategies for previous sections, the CR stated that Embase and EconLIT were not searched for the cost-effectiveness section, due to lack of access. The databases are required for inclusion by the NICE Specification for the Manufacturer's Submission.[19] It is important to search Embase as well as PubMed due to the differences in their coverage. The largest component of PubMed is Medline and approximately 1,800 of the journals indexed in Embase are not indexed in Medline.[25] The ERG felt that Embase would have been particularly useful for this submission, due to Embase's pharmaceutical and European focus to its content.

The date and span of searching was reported for PubMed and CRD, but this information was not provided for the Cochrane Collaboration/Library search. The searches were reported clearly to enable replication.

The first PubMed search was well constructed using Boolean logic and correctly combined an intervention facet (mannitol) with a population facet (CF) and a study design facet (cost effectiveness). The ERG felt that the mannitol facet could have been improved by incorporating truncation, synonyms and a CAS number. The CF facet did not use any free text terms, instead relying solely on a subject heading. Relying solely on subject headings in search facets is not good practice as highlighted in the Cochrane Handbook[26] which cautions searchers against the assumption that all articles will be indexed correctly or in line with the searcher's expectations. A wide variety of text terms should be used to supplement subject headings.

The second search removed the mannitol facet to increase sensitivity. The third search was almost identical to the second except that it used the NOT operator to remove all articles with "screening" or "diagnosis" in the title or abstract. The Cochrane Handbook recommends that the NOT operator should be avoided where possible due to the possible removal of relevant records[27]. In this case, it could be foreseen that relevant cost effectiveness studies might reference screening or diagnosis in the title or abstract and thus be missed. This did not impacted negatively on retrieval because this search's results were a subset of search two and the MS stated that results from the second search were screened as well, therefore the ERG was unclear why the third search was undertaken.

An unreferenced cost effectiveness (CE) filter was used in these searches. It contained this section: "cost effectiveness"[Title/Abstract] OR cost[Title/Abstract]. The former phrase is rendered redundant by the latter. The PubMed database provides cost and economic filters that have been adapted from objectively derived filters and utilising one or both of those would have been more appropriate for these searches[28].

An English language and date limit (1990 onwards) were added to the PubMed searches. This appeared to contradict the manufacturer's opening statement of intent in this chapter to "identify any existing cost-effectiveness studies in the field of CF". No rationale was given for the date limit however; some was given for the language in the CR (page 36). The manufacturer conducted a separate wave of searches for studies written in five other European languages, the second search inexplicably retrieving fewer studies than the third, given that the third was simply a subset of the second. The ERG was unclear why the manufacturer decided again in the second search to limit to just five languages as this might have introduced bias into the results. The Cochrane Handbook advises against searching using language limits and afterwards to make decisions about including non-English studies on a case-by-case basis[29].

The table below illustrates how using a more sophisticated search strategy and CE filter, removal of unnecessary limits and searching all important databases (e.g. Embase), increased the retrieval many times over. The ERG considered it very likely that relevant CE studies may have been missed; however the ERG was unable to screen the additional references due to time constraints.

Table 2: Comparison of retrieval between manufacturer and ERG searches for cost effectiveness

	Details	Studies retrieved
Updated manufacturer searches + mannitol facet		
PubMed (1st search) up to 01.04.11	+ Unreferenced filter + limits	0
ERG searches + mannitol facet		
Embase 1980-2011 wk 12	+ CRD's NHS EED filter	14
Medline 1948-2011, March, Week 3	+ CRD's NHS EED filter	0
PubMed up to 30.03.11	+ PubMed's economics filter	1
PubMed up to 30.03.11	+ PubMed's costs filter	2
Updated manufacturers searches without mannitol facet		
PubMed (2nd search) up to 01.04.11	+ Unreferenced filter + limits	198
PubMed (3rd search) up to 01.04.11	+ Unreferenced filter + limits	104
ERG searches without mannitol facet		
Embase 1980-2011 wk 12	+ CRD's NHS EED filter	1136
Medline 1948-2011, March, Week 3	+ CRD's NHS EED filter	27

PubMed up to 30.03.11	+ PubMed's economics filter	305
PubMed up to 30.03.11	+ PubMed's costs filter	658

The manufacturer reported searching the CRD database for cystic fibrosis and cost effectiveness without attempting to include a mannitol facet. The ERG was concerned this search incorporated the term "cost effectiveness" within the NHS EED search. NHS EED is a database which is specifically made up of economic evaluations; therefore this filter was not necessary. Using a CE filter on DARE and HTA was acceptable, but NHS EED should have been searched separately. The ERG searched NHS EED without "cost effectiveness" as a qualifying term and retrieved 86 records compared to 47 from an updated search using the manufacturer's strategy.

Two additional searches were reported in this section on pages 137 and 142. Both were searches for data for use in the economic model and while basic, the ERG considers them adequate. However as with many other searches in this section, these strategies could have employed many more synonyms and used text terms for cystic fibrosis. As mentioned previously, the ERG felt that application of an English language limit was unnecessary.

4.1.1.5 Health Related Quality of Life (HRQL)

The manufacturer searched PubMed - which covers Medline and Medline In-Process – and CRD databases which include NHS Economic Evaluation Database (NHS EED), but did not search the NICE required EconLIT or Embase databases due to lack of access (CR page 36). An additional search was undertaken to search for data held by Pharmaxis but no specific strategy or details were provided for the ERG to critique.

The search concepts were stated as "health utility impact" combined with "cystic fibrosis". As previously, the search contained a revision taken, as an initial search line including a mannitol facet retrieved zero articles. This strategy alteration should have appeared in the main report text as well as the appendix.

Two other "key issues" were highlighted in the introduction; pulmonary exacerbations and lung transplantation. These concepts were not included in any of the MS searches and the ERG believed this to be an unnecessary omission.

The PubMed search was syntactically and structurally sound and two relevant subject headings were used along with text terms. The search strategy was straightforward to replicate by the ERG.

The cystic fibrosis facet and HRQOL facet contained only subject headings without text, which may have reduced sensitivity. The ERG identified several additional instrument and HRQOL terms, synonyms and variants that could have been used to increase sensitivity. Some examples, adapted from Paisley (2005)[30] are listed below:

"cystic fibrosis questionnaire" or "CFQ"

"short form 36" or "sf36"

”hqol” or “h qol”

The search would have retrieved much more relevant results with the use of these terms and the employment of a measurement instruments filter. The ERG utilised an HRQL search filter in the comparison searches.

The ERG created an HRQOL search on PubMed containing the filter and synonyms mentioned in the critique above. This search retrieved 443 hits, more than double the 192 hits retrieved by re-running the manufacturer search.

As in some previous searches, the MS searches were limited to English language in the first instance with a second search carried out which was limited to five other European languages. The ERG felt that the inclusion of a language limit might introduce bias into the search results[29]

There were some inconsistencies in reporting the main text of the submission. The MS indicated a 10 year limit was applied, resulting in 119 references retrieved. However, the search in the appendix was date limited from 1990 to present and reported 177 references retrieved. This was explained by the manufacturer on page 37 of the CR as an error. The CR stated that the strategy and results on page 148 were that of an earlier search and should have been changed to match the MS appendix 12 (page 234).

The CR reported a search was undertaken using CRD databases, including NHS EED. The search began with a mannitol facet but this was removed due to low retrieval. The search itself could have been improved through the use of the HRQOL terms, synonyms and variants mentioned earlier in this section. The CR search relied on the phrase “quality of life”, which failed to take into account abstracting and indexing variations. The ERG formulated a new strategy and retrieved 348 papers compared to 80 from an update of the manufacturer’s search.

4.1.1.6 Resource Identification, measurement and valuation

The search undertaken in section 6.5.1 was redundant, considering the cost effectiveness searches in section 6.1.1. The ERG’s comments on the cost-effectiveness searches also applied to this section. Furthermore, the searches in this section did not contain any text terms, and the cost effectiveness filter was overly simplistic as it comprised of a single subject heading.

There was an error in reporting on page 235. The search box indicated 30 hits whilst the text clearly stated that 32 items were identified.

4.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

1. Review of mannitol studies

The inclusion and exclusion criteria used in the selection of evidence for the systematic review were presented in table 3 (page 28) of the MS. The table in the MS was labelled as 'eligibility criteria used in search strategy' but was presented within the description of the study selection process (Section 5.2.1). It was not clear from the MS how many reviewers were involved in the study selection process. Best practice specifies that two reviewers be involved in the application of the inclusion and exclusion criteria in order to limit bias in study selection. Details of the inclusion and exclusion criteria applied in the MS are presented in Table 3.

Table 3: Inclusion/exclusion criteria used in study selection (as presented by the manufacturer)

	Inclusion criteria	Exclusion criteria
First phase	Population: Patients with cystic fibrosis Interventions: Bronchitol or Bronchitol Study design: randomised clinical trial Language restrictions: English language only	
Second phase		Population: Paediatric or adolescent patients only Interventions: Doses of Bronchitol / Bronchitol not at therapeutic dose (i.e. not at ≈400mg BD); different formulation to that being licensed.

Comparators were not specified, indicating that all comparators were included. The interventions were described as "Bronchitol or Bronchitol"; this should probably be "Mannitol or Bronchitol". The search strategy in appendix 2, though limited, does include the word 'mannitol'. The MS stated that only RCTs were included in the analysis. It was not explicitly stated in the MS whether both phase II and phase III clinical trials were eligible for inclusion. The ERG considers non-RCTs to be a valid and important source of evidence for the evaluation of adverse events. Controlled clinical trials may exclude patients at high risk from harm,[31] may be too short in terms of follow-up to detect long-term harm, may not have sufficiently large sample sizes to detect uncommon adverse events, or may not have reported them in a consistent manner.[32-35] The MS stated on page 82, that "Relevant non-RCT data come for this appraisal come from the open label extension phase of one of the pivotal clinical trials" (a 26 week open label phase of study 301). The MS does not provide a search strategy or an explanation why these were the only data included in this section. Data for relevant comparators were not searched either. It is possible that other non-RCT evidence may be available for the intervention as well as the comparator drugs which were not identified.

Most outcomes listed in the decision problem were present in the tabulated results in the MS (section 5.5). Mortality was not measured in the two studies and is therefore not reported; although it is included in the economic model in chapter 6 of the MS.

The exclusion of studies not available in English was a reasonable decision on the basis of available time. The potential implications of this decision were not discussed.

The most important problem with the MS is that outcomes are primarily reported for the full trial population: CF patients aged 6 years or older and RhDNase users and non-users combined. Separate data are reported for adults, as well as for RhDNase users and non-users; and a few data are reported for one of the two relevant populations: adult CF patients who are RhDNase users. No data are reported for the second relevant population: adult CF patients who are ineligible, intolerant, or inadequately responsive to rhDNase; instead the MS uses data for adult CF patients who are RhDNase non-users, which is not the same as ineligible, intolerant, or inadequately responsive to rhDNase. In fact it is stated in the MS that "the rhDNase user population had more severe CF disease at baseline compared with non-users" (MS, page 16). Therefore, it is possible that a large proportion of the non-users do not use RhDNase for other reasons than ineligibility, intolerance, or inadequate response.

Complete data for the relevant populations were requested from the manufacturer, together with analyses in the appropriate populations. However, only data for lung function and exacerbations were provided for the relevant populations.

2. Mixed treatment comparison

For the comparison mannitol versus BSC, the MS uses data from head-to-head comparisons (study 301 and 302). For the comparison mannitol versus hypertonic saline, the MS describes a feasibility study to assess whether an indirect comparison is possible.

The inclusion and exclusion criteria used in the selection of evidence for the indirect comparison were presented on page 81 of the MS. Again, it was not clear from the MS how many reviewers were involved in the study selection process. Best practice specifies that two reviewers be involved in the application of inclusion and exclusion criteria in order to limit bias in study selection. Details of the inclusion and exclusion criteria applied in the MS are presented in Table 4.

Table 4: Inclusion/exclusion criteria used in study selection (as presented by the manufacturer)

	Clinical effectiveness
Inclusion criteria	• Patients with CF diagnosed clinically or by sweat and genetic testing, including all degrees of disease severity • Treatment with hypertonic saline or Bronchitol (~400mg BD) • Prospective randomised controlled trials (RCTs)
Exclusion criteria	• None

The literature search to identify studies which would potentially be relevant for an indirect comparison retrieved 10 studies, these studies are described in appendix 5 (MS, page 221). The appendix has the title "Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)", although no quality assessment for these trials is reported.

Two studies were found for mannitol versus control (study 301 and Jaques 2008[36] (=study 201)). It is not clear why studies found through the original search for mannitol studies, such as study 302, 202, 203 and Robinson et al. 1999,[37] were not found in this search. In addition, eight studies were found comparing hypertonic saline with control. Most of these were short term (1 day to 2 weeks) cross-over trials; only one study had a duration of more than 2 weeks: Elkins 2006.[17] This was a randomised double-blind controlled parallel trial, including 164 CF patients, aged 6 years and older, comparing hypertonic saline (7%) 4ml bd with saline (0.9%) for 48 weeks.

The MS concludes that an indirect comparison of mannitol and hypertonic saline was not felt to be an appropriate analysis in this situation. The main reason being, "the absence of a common control arm between the respective randomised controlled trials". The MS states, that the low dose (50mg) formulation of mannitol (control as used in study 301 and 302) may show some degree of clinical activity which would preclude its use as a common link to the hypertonic saline RCTs (control reported to be 0.9% saline (isotonic saline) as in 7/8 studies). Other limitations mentioned in the MS were differences in inclusion/exclusion criteria and baseline study characteristics between trials.

4.1.3 What studies were included in the clinical effectiveness review and what were excluded?

Provide a table of identified studies. Please identify the <u>most important</u> clinical effectiveness studies.

<u>1. Review of mannitol studies</u>

The flow diagram in the MS (Fig. 1, page 30) shows that 2 RCTs were included (studies 301 and 302). Details of the studies and their populations as presented in the MS (Tables 7 to 17, pages 34 to 57) are presented in Table 5.

Table 5: Studies included in the systematic review of mannitol studies.

Trial no. (acronym)	Design	Intervention, Comparator	Population	Key inclusion criteria
DPM-CF-301	Randomised, multicentre, controlled, parallel group double-blind 26-week safety and efficacy phase followed by a 26-52 week open label safety phase	Bronchitol 400mg BD versus Bronchitol 50mg BD	People with CF, aged ≥6yrs with FEV1 >30 and <90% predicted; no concomitant hypertonic saline use; negative Bronchitol tolerance test (MTT).	• Confirmed diagnosis of cystic fibrosis • Subjects aged ≥6 years of age • FEV_1 >30% and <90% predicted • Able to perform techniques necessary to measure lung function
DPM-CF-302	Randomised, multicentre, controlled, parallel arm, double blind 26-week treatment, followed by 26 weeks of open label treatment	Bronchitol 400mg BD versus Bronchitol 50mg BD	People with CF, aged ≥6yrs with FEV1 >40 and <90% predicted no concomitant hypertonic saline use; negative Bronchitol tolerance test (MTT).	• Confirmed diagnosis of cystic fibrosis via sweat test and/or genotype • Subjects aged ≥6 years of age • FEV_1 >40 % and <90% predicted • Able to perform techniques necessary to measure lung function

Four other mannitol trials were excluded:

- Studies 201 & 202: Although studies DPM-CF-201 and DPM-CF-202 do provide data on both adult and paediatric/ adolescent patients, the studies are too small to be able to extract meaningful data in the adult only population and only assess treatment effects over a 2 week period. In addition, DPM-CF-201 included a formulation of mannitol which is different to the one which has been submitted for regulatory approval and DPM-CF-202 was designed as a dose finding study. However, according to the manufacturer, these studies provide useful supporting data in the wider CF population (which includes adult patients) and therefore a summary of the study designs along with key outcomes data are presented in Appendix 18 of the MS.

- Study 203 was in paediatric/ adolescent patients only.

- Robinson et al. 1999.[37] This was a randomised cross-over trial comparing 4 treatment arms with a duration of 4 days (1 day per treatment): mannitol (300 mg), hypertonic saline, isotonic saline and placebo.

COMMENT

The ERG agrees that studies 301 and 302 are the main source of evidence for this appraisal. Studies 201 and 202 are less useful due to their short duration (2 weeks), study 203 is in children only, and Robinson et al. 1999[37] used a lower dose of mannitol and treatment duration was only one day.

2. Mixed treatment comparison

Regarding the relevant comparisons:

1. Mannitol versus best supportive care – there is direct evidence from two RCTs (studies 301 and 302).

2. Mannitol versus hypertonic saline – there is one head-to-head comparison[37]. However, the lower dose of mannitol (300mg), one-day treatment duration and inclusion of only 12 patients makes it impossible to use the study for this appraisal.

   The alternative is an indirect comparison of mannitol versus hypertonic saline, using the placebo/BSC arm as the common comparator. However, in the MS this possibility is dismissed because "The low dose formulation of Bronchitol (control as used in DPM-CF-301 and DPM-CF-302) may show some degree of clinical activity which would preclude its use as a common link to the hypertonic saline RCTs (control reported to be 0.9% saline (isotonic saline) as in 7/8 studies)", and "Other limitations which were observed were differences in inclusion/exclusion criteria and baseline study characteristics between trials." (MS, page 81).

When we asked the manufacturer to clarify why they think mannitol 50mg is sub-therapeutic in this population and at the same time may show some degree of clinical activity, the manufacturer responded:

Pharmaxis agrees that the argument above was not correctly formulated. Indeed, while low dose of mannitol (40 – 50 mg) may have some degree of clinical activity in children, it has been shown to be sub-therapeutic in adults in the dose-response study (DPM-CF-202) and in both phase III studies.

Nevertheless, the main argument for not comparing mannitol to hypertonic saline was not the absence of a common control arm, but rather to significant differences in the design and target population between the mannitol and the hypertonic saline studies. Of the eight RCT with hypertonic saline, only three were conducted solely in adults [Robinson 1996, 1997, 1999]. The sample size of these three studies was very small (n = 10 – 12) and the treatment period duration was only one day in each study. Two additional studies were published only as abstracts [Button 1996; Chadwick 1997] and the treatment period was also significantly shorter than in the mannitol studies. The studies of Eng [Eng 1996] and of Riedler [Riedler 1996] had also a short treatment duration and in the latter study all patients (n = 10) were adolescents.

The only study that may have been pertinent for indirect comparison was the trial of Elkins et al (c.f., reference 29 of submission dossier). This study included children, adolescents and adults, but only data for the overall population was available. Importantly, this population did not appear to be optimally treated, based on current standard of care. Comparison between the overall population of the Elkins study and the adults from the mannitol studies was not deemed appropriate. Indirect comparison of the overall population from these studies was not feasible either, due to the low beneficial effect of low dose mannitol in children. Furthermore, as shown in the table below, baseline characteristics also differed between studies, particularly in terms of baseline FEV_1 predicted values, proportion of patients with pseudomona aeruginosa infection and antibiotic use.

Table 6: Trials found through the indirect comparison feasibility study

Reference	Intervention	Patient group	Patient number	Outcomes	Study design
Bronchitol® versus Control					
Bilton, 2009 ECFC and NACFC Poster (CF301)[38]	Bronchitol (inhaled dry powder Mannitol) 400mg bd for 26 weeks Control	CF patients; mean age = 23.1(11.6) and 22.8(10.75)years resp; FEV1=62.4(16.45)% and 61.4(16.13)% resp; NO hypertonic saline allowed.	N=177 N=118	Change in FEV1; FVC; PEF	Multicenter, randomised, double-blind, placebo controlled study
Jaques, 2008[36]	Mannitol (420mg) 1st arm bd vs. Control for 2 weeks	Clinically stable CF patients; mean age=18.9 and 19.3	N=21	Change in FEV1; FVC	Randomised, double-blind, placebo

Reference	Intervention	Patient group	Patient number	Outcomes	Study design
	Mannitol (420mg) 2nd arm bd vs. Control for 2 weeks	years resp.; FEV1 predicted=64.9(13.6)% and 64.4(11.8)% for Grp A and Grp B resp.	N=18		controlled, crossover study
Hypertonic saline versus Control					
Button, 1996 Study 2 Abstract[39]	Hypertonic saline (6%) 10ml via ultrasonic nebuliser bd for 2 weeks Isotonic saline (0.9%) 10ml via ultrasonic nebuliser bd 2 weeks	CF patients; mean age=16.2 (7-36)	N=52	FEV1	Randomised crossover trial
Chadwick, 1997 Abstract[40]	Isotonic saline Hypertonic saline (3.5%) Hypotonic saline	Clinically stable CF patients	N=15	FEV1; Nebulisation	Single-blind, randomised, cross-over trial
Elkins, 2006[17]	Hypertonic saline (7%) 4ml bd for 48 weeks Control; Saline (0.9%) for 48 weeks	Clinically stable CF; mean age= 18.4(9.3) and 18.7(9.2) years resp; FEV1%predicted= 73(21)% and 76(21)% resp;	N=83 N=81	FEV1; FVC; FEF25-75	Randomised, double-blind controlled, parallel trial
Eng, 1996[41]	Hypertonic saline (6%) 10ml bd for 2 weeks Isotonic saline (0.9%) bd for 2 weeks	CF patients; mean age=16.2(7-36)years; confirmed diagnosis of CF by sweat chloride above 60mmol/L; clinically stable lung disease; FEV1 (predicted)=30% to 70%	N=27 N=25	Change in FEV1; FCV; VAS scale for dyspnoea; fatigue; appetite	Open, parallel, randomised controlled trial
Riedler, 1996[42]	Hypertonic saline (6%) daily for 2 days Isotonic saline (0.9%) daily for 2 days(cross-over)	CF patients; Predicted FVC=72% (15%-85%); FEV1= 53.5% (41%-73%); Mean age= 16.5 (13-20)	N=10	Sputum expectoration; VAS; Feeling of cleared chest	Randomised cross-over trial

Reference	Intervention	Patient group	Patient number	Outcomes	Study design
Robinson, 1996[43]	Amiloride 3mg for 1 day Hypertonic saline+Amiloride for 1 day Isotonic saline for 1 day	CF patients; mean age=21.9(3.0)years; Predicted FEV1 (mean)= 60.8%; FCV (mean)=77.4%	N=12	Sputum isotope clearance; Mucociliary clearance; Change in FEV1	Randomised cross-over trial
Robinson, 1997[16]	Hypertonic saline (3%) for 1 day Hypertonic saline (7%) for 1 day Hypertonic saline (12%) for 1 day Control: Isotonic saline (0.9%) + Cough for 1 day	Clinically stable CF; Mean age= 22.1years (3.8) range 19-28 years; FEV1 52.0 (6.7)%	N=10	FEV1; Sputum clearance; Mucociliary clearance	Randomised, cross-over trial
Robinson, 1999[37]	Hypertonic saline (6%) 7ml for 1 day Isotonic saline (0.9%) for 1 day Mannitol (300mg) encapsulated for 1 day Empty capsules for 1 day	Clinically stable CF; mean age 29.9(9.4); FEV1 60.2(16.5)%; FVC 78.8(16.5)	N=12	FEV1; Sputum clearance; Mucociliary clearance	Randomised, cross-over trial

COMMENT

The ERG agrees that results from studies with a duration of 2 weeks or less are not comparable with 26 weeks results from the mannitol studies. This rules out 7 of the 8 studies found through the indirect comparison feasibility study (see table 6), leaving only Elkins[17] as a possibility for an indirect comparison of mannitol versus hypertonic saline.

The ERG also agrees that there is heterogeneity between populations in the Elkins[17] and mannitol trials. However, as hypertonic saline is mentioned in the NICE scope as the main comparator, the ERG would like to present a comparison based on the best available evidence. However, the limitations of this indirect comparison, as described by the manufacturer (Response to clarification letter, pages 13-15) should be kept in mind when interpreting the results. See section 4.2.7 for this indirect comparison of mannitol versus hypertonic saline.

4.1.4 Provide details of any relevant studies not discussed in the submission? Why were these studies excluded and how were these studies identified by the ERG?

1. Review of mannitol studies

The ERG created new searches for clinical effectiveness. Retrieval for the Medline and Embase strategies were more than double that of the manufacturer's. The ERG was not able to screen search results due to time constraints and therefore cannot give a definitive indication that relevant studies were missed.

2. Mixed treatment comparison

The ERG re-ran the manufacturer Medline, Embase and Cochrane Library mixed treatment saech strategies. The mannitol facet was removed to leave studies investigating hypertonic saline for CF; the 123 resulting papers were screened by reviewers but no relevant studies were found.

4.2 Summary and critique of submitted clinical effectiveness evidence

If there is more than one RCT described in the MS, it may be appropriate to discuss each trial individually using the headings described.

4.2.1 Summary of submitted clinical evidence for each relevant trial.

1. Review of mannitol studies

Results of the two included mannitol studies are described in section 5.5 (pages 57-78). However, most results are not specifically reported for the interventions and populations of interest for this appraisal: (1) Mannitol in combination with rhDNase for all adult CF patients; and (2) Mannitol alone for adult CF patients who are ineligible, intolerant or inadequately responsive to rhDNase. Instead, results are reported for all adults, irrespective of rhDNase use. In addition, subgroup analyses are reported for rhDNase users (MS, page 69-73), but these data were not reported separately for adults only; and subgroup analyses are reported for adults (MS, page 73-76), but these data were not reported separately for rhDNase users.

The only data reported from the two pivotal trials relevant to the population described in the scope are in Table 29 (MS, page77). Here change in FEV1, % change in FEV1, change in predicted FEV1 and change in FVC from baseline are reported separately for adult rhDNase users and non-users. No data are reported for adult CF patients who are ineligible, intolerant or inadequately responsive to rhDNase.

No data for either population are reported for mortality, exacerbations, respiratory symptoms, exercise tolerance, adverse events and quality of life.

In the clarification letter we asked the manufacturer to provide separate data for the two populations described in the scope. In their response the manufacturer provided data for change in FEV1 (a graph

only) and exacerbations. The data that could be derived from the industry submission and the response to our questions is summarised in the table below.

Table 7. Data for the relevant populations as described in the scope

Outcome	Effect of mannitol in combination with rhDNase in adults	Effect of mannitol alone in adults who are ineligible, intolerant or inadequately responsive to rhDNase
Mortality	NR	NR
Exacerbations: **- PDPE incidence**	301: RR = 0.76 (0.43, 1.34)*** 302: RR = 1.92 (0.66, 5.56) Pooled: RR = 1.00 (0.61, 1.66)	301: RR = 0.54 (0.17, 1.70)*** 302: RR = 0.31 (0.07, 1.46) Pooled: RR = 0.44 (0.18, 1.10)
- PDPE rate per year	301: Rate ratio = 0.89 (0.57, 1.40)*** 302: Rate ratio = 4.37 (1.53, 12.48) Pooled: Rate ratio = 1.14 (0.75, 1.73)	301: Rate ratio = 0.64 (0.18, 2.27)*** 302: Rate ratio = 0.30 (0.05, 1.81) Pooled: Rate ratio = 0.50 (0.18, 1.40)
Lung function: **- Change in FEV1**	301: MD = 109.27 (52.77, 165.77)** 302: MD = 88.45 (-8.46, 185.36) Pooled: MD = 103.99 (55.18, 152.80) 301: MD = 93.95 (*15.58, 172.32*)*** 302: MD = 88.45 (*-8.39, 185.29*) Pooled: MD = 91.77 (30.85, 152.69)	 301: MD = 146.98 (*19.42, 274.54*)*** 302: MD = 208.60 (*-13.00, 430.20*) Pooled: MD = 162.32 (51.77, 272.87)
- % change in FEV1	301: MD = 4.19 (0.31, 8.07)** 302: MD = 5.43 (-0.40, 11.31) Pooled: MD = 4.57 (1.33, 7.80)	
- % predicted FEV1	301: MD = 2.66 (0.59, 4.73)** 302: MD = 2.95 (-0.61, 6.50) Pooled: MD = 2.73 (0.94, 4.52)	
- FEV1 responders	NR	
- FVC	301: MD=117.42 (1.00, 233.85)** 302: MD=96.94 (-7.68, 201.55) Pooled: MD = 106.09 (28.27, 183.91)	
Respiratory symptoms	NR	NR
Exercise tolerance	NR	NR
Adverse events	NR	NR
Quality of Life: **- CFQ-R**	NR	NR

* Data are presented as LSmean (SD) or LSmean (95% CI) and are based on change from baseline to post baseline (weeks 6-26);
** Data from MS, table 29, page 77.
*** Data from response to clarification letter, Figure 2, page 4 (95% CI is estimated from graph for data in italics; for risk ratios SE (and corresponding CI) is calculated using the formula for calculating SEs for risk ratios from the Cochrane Handbook (Chapter 9.4.8) assuming 26 weeks of follow-up for all participants.
PDPE=Protocol defined Pulmonary Exacerbations; RR=Relative Risk; MD = Mean Difference
Lung function: MD>0 favours mannitol; Exacebations: RR<1 favours mannitol; MD<0 favours mannitol.

As can be seen in the table above, data for mortality, respiratory symptoms, exercise tolerance, adverse events and quality of life are not reported. Exacerbations showed no significant differences between mannitol and control in either population. Lung function outcomes reported for study 301 all showed

significant results in favour of mannitol. However, lung function outcomes reported for study 302 all showed non-significant results for mannitol compared with control for both populations. The pooled results for lung function outcomes all showed significant differences in favour of mannitol.

There are also inconsistencies in the data reported. In the MS, change in FEV1 is reported as MD=109.27 (52.77, 165.77); in the response to the clarification letter this is: MD=93.95 (NR). In table 30 (MS, page 79), the manufacturer presents data for % predicted FEV1 in adult rhDNase users for both studies and combined. The combined result looks unlikely as the combined mean (2.36) is lower than both means in the two individual studies (2.66 and 2.95, respectively); the combined mean would most likely be in between the individual study means. Therefore, we will focus on our own pooled calculations.

We checked the clinical study reports (CSRs) for both studies, but were unable to find data for adult RhDNase users and adult CF patients who are ineligible, intolerant or inadequately responsive to rhDNase. Data were reported in both reports for rhDNase users and non-users, but not for adults.

Data for adverse events in the adult population were reported in the MS (MS, Tables 48-51, page 102), but not separately for rhDNase users. Separately, the manufacturer also reported adverse events for rhDNAse users, but these data were for all age groups (MS, page 99-102). Generally, rhDNase users seem to have more adverse events than rhDNase non-users.

2. Mixed treatment comparison

There are no data reported for trials comparing other interventions.

4.2.2 Describe and critique the manufacturer's approach to validity assessment for each relevant trial.

1. Review of mannitol studies

The table below is Table 17 from the MS (MS, page 56).

Table 8: Quality assessment of included RCTs

Issue	Study 301	Study 302
Was randomisation carried out appropriately?	YES	YES
Was the concealment of treatment allocation adequate?	YES	YES
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	YES	YES
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	YES	YES
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	YES[a]	NO
Is there any evidence to suggest that the authors measured more outcomes than they reported?	NO	NO

Issue	Study 301	Study 302
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	YES	YES
Responses noted as Yes, No, Not clear or N/A. a unbalanced but additional analyses suggested no impact on primary outcomes		

COMMENT

Generally, the ERG agrees with the quality assessment reported in the table above. Regarding outcomes reported, although all outcomes were reported for the total population, they were not reported for the two populations of interest for this appraisal.

2. Mixed treatment comparison

No studies were included for the MTC.

4.2.3 Describe and critique the statistical approach used within each relevant trial.

1. Review of mannitol studies

The statistical analyses in the included studies is described in Table 13 (MS, page 48) and copied below.

Table 9. Statistical analyses in the relevant RCTs

	DPM-CF-301	DPM-CF-302
Hypothesis objective	To determine the effect of Inhaled Dry Powder Mannitol compared to control on FEV_1 in subjects with Cystic Fibrosis (CF)	To determine whether inhaled mannitol compared to control improves FEV_1 in patients with cystic fibrosis (CF).
Statistical analysis for primary endpoint	Change from baseline in FEV_1 was assessed using mixed models repeated measures analyses (MMRM) in SAS. Change from baseline in FEV_1 values were the outcome variables. Included covariates were: Treatment group, rhDNase use, region (Europe vs. not), study week, disease severity (% predicted FEV_1 at screening), age, baseline spirometry value and gender.	FEV_1 was analysed using mixed model repeated measures (MMRM) methodology with subject fitted as a random effect and an unstructured variance-covariance structure. Two analyses were carried out: difference between treatments in change from baseline (across all timepoints) and difference between treatments in change from baseline to each timepoint. Included covariates were: Treatment group, rhDNase use, region (Argentina, Belgium/Netherlands, Canada, France, Germany, Netherlands, USA), study week, disease severity (% predicted FEV_1 at screening), age, baseline spirometry value and gender.

Sample size, power calculation	• A total sample size of 109 subjects in the Bronchitol arm and 73 subjects in the control arm taking concurrent rhDNase would give the study 80% power to detect a difference of 85mL in change from baseline of FEV1 between the Bronchitol and control arms at 26 weeks in this subgroup of subjects • with 50% more subjects in each arm of the study when not restricted to subjects currently taking rhDNase, the study has 80% power to detect a difference of 70mL in change from baseline of FEV_1 between the Bronchitol and control arms at 26 weeks. • The study also has more than 80% power to detect a difference in rates of pulmonary exacerbations over the course of a 26 week study, assuming pulmonary exacerbation rates of 0.42 events per subject-year in subjects treated with Bronchitol, and 0.96 events per subject-year in subjects in the control group.	• A total sample size of 300 subjects was planned with 180 randomised to Bronchitol and 120 to control. An estimated 65% of subjects were expected to be taking rhDNase. With a dropout rate of 30%, 126 subjects in the Bronchitol arm were expected to complete the study (84 taking rhDNase, 42 not taking rhDNase), and 84 subjects in the control arm were expected to complete the study.
Data management and patient withdrawals	Using a mixed model for analysis utilizes all data for all subjects and provided missing values can be viewed as missing at random missing data do not need to be imputed. The pattern of withdrawal was explored through Kaplan Meier plots. With no emphatic evidence to suggest that values are not missing at random and therefore the mixed model with no imputation can be considered unbiased.	All data contained in the database are listed. Using a mixed model for analysis utilizes all data for all subjects and provided missing values can be viewed as missing at random missing data do not need to be imputed. In order to address any impacts of missing data on the primary endpoint and the robustness of the primary endpoint estimate, sensitivity analyses (ANCOVA) using 2 different missing data imputation methods was carried out: • Carrying forward the last available post-baseline observation • Carrying forward the baseline observation for subjects who do not have a valid Visit 4/Week 26 FEV_1 measurement
This table includes items 6a and 6b from CONSORT checklist These analyses are in line with SAPs which were finalized before study unblinding.		

COMMENT

Apart from the fact that analysis were not presented separately for the two populations of interest for this appraisal, the statistical analyses in both studies seem sound.

2. Mixed treatment comparison

No studies were included for the MTC.

4.2.4 Describe and critique the manufacturer's approach to outcome selection within each relevant trial.

1. Review of mannitol studies

The key outcomes from the two included studies are described in Table 12 (MS, page 42). This table is reproduced below.

Table 10: Primary and secondary outcomes of the included studies

Study	Primary outcomes and measures	Secondary outcome(s) and measures
DPM-CF-301	Change in absolute FEV_1 over 26 weeks compared to control	• Change in FEV_1 by existing rhDNase treatment[a] • Proportion of subjects who "respond" on the basis of FEV_1 (overall and by rhDNase stratum)[b] • Proportion of subjects who "respond" on the basis of quality of life (overall and by rhDNase stratum)[b] • Reduction in pulmonary exacerbations (overall and by rhDNase stratum)[a] • Improvement in quality of life (overall and in each rhDNase stratum)[a] • Reduction in days on IV antibiotics, rescue oral or inhaled antibiotics • Reduction in hospital days due to pulmonary exacerbations • Other measures of lung function • Safety profile: adverse events, haematology, biochemistry, change in bronchodilator response, sputum microbiology, physical examination • • Reduction in hospital and community care costs[c]
DPM-CF-302	FEV_1 change from baseline (mL) compared to control	▪ Change in FEV_1 by existing rhDNase treatment ▪ Reduction in pulmonary exacerbations (overall and by rhDNase stratum)[a] ▪ Improvements in quality of life ▪ Reduction in days on IV antibiotics, rescue oral or inhaled antibiotics ▪ Reduction in days in hospital due to pulmonary exacerbations ▪ Improvements in other measures of lung function[d] ▪ Safety profile (adverse events, haematology, biochemistry, sputum microbiology (both qualitative and quantitative), physical examination, including vital signs) ▪ Reduces hospital and community care costs[c] ▪ Sputum weight[b]
This table includes items 6a and 6b from CONSORT checklist a minor adjustment from protocol to include both strata b additional item not in protocol however was included in the statistical analysis plan (SAP) c not addressed in this section d change in % predicted FEV_1 was not in protocol however was included in the statistical analysis plan (SAP)		

COMMENT

All relevant outcomes as described in the scope, except for mortality, are listed in the table above. According to the statement of the decision problem (MS, Chapter 4, page 25) "improvement in respiratory symptoms" was covered by the respiratory domain of the CFQ-R and "improvement in exercise tolerance" was covered by the physical domain of the CFQ-R. Mortality was not assessed in either trial, despite it being mentioned as an included outcome in the statement of the decision problem (MS, Chapter 4, page 25). No justification in the MS was provided for this omission.

However, the main problem relating to the outcomes reported is the fact that only lung function is reported in the MS for one of the relevant populations for this appraisal: adult rhDNase users (MS, Table 29, page 77). In response to the clarification letter, the ERG received data for both populations, adult rhDNase users and adults who are ineligible, intolerant, or inadequately responsive to rhDNase, for change in FEV1 (graphs only) and exacerbations. No other data were provided, despite our request for all relevant data for the specific populations. This means the ERG has no data relating to the relevant populations for the following outcomes: mortality, respiratory symptoms, exercise tolerance, adverse events and quality of life.

2. Mixed treatment comparison

No studies were included for the MTC.

4.2.5 To what extent does each relevant trial include the patient population(s), intervention(s), comparator(s) and outcomes as defined in the final scope?

1. Review of mannitol studies

Population

The two included studies had inclusion criteria that were in accordance with the population defined in the scope. In the scope the population is described as "people with cystic fibrosis". However, after having read the MS and discussion with NICE it was agreed that the relevant population should be as defined in the MS: "Adults (18 years and above) with cystic fibrosis". The justification for this in the MS was: "Current label of Bronchitol is restricted to adults; hence the base case analysis will be performed on adults. The entire population (age 6>) as well as different age groups will be modelled as a separate scenario" (MS, Chapter 4, page 25).

This means that the population in the two included studies no longer matches the population defined in the scope. Instead, only a subset of the study populations (adults with CF) is relevant for the scope.

Intervention

The intervention in the two included studies is in accordance with the intervention described in the scope: "Mannitol dry powder for inhalation". The MS adds to this that "Bronchitol is given in addition to best supportive care with or without rhDNAse." (MS, Chapter 4, page 25).

In fact, the latest information regarding the license indication for Bronchitol from the manufacturer is: *The EMA process is still ongoing; an oral hearing with CHMP is likely to take place in May 2011. The European Marketing Authorisation Application (MAA) seeks to gain regulatory approval for Bronchitol as a: "treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to rhDNase, and in adults ineligible, intolerant, or inadequately responsive to rhDNase"*

No further information was provided at the time this ERG report was completed.

Given the information from the manufacturer, there are now two distinct interventions for two separate populations: (1) Mannitol in combination with rhDNase for adults with cystic fibrosis, and (2) Mannitol alone for adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase.

Comparators

The comparators described in the scope are: "The following treatments used alone or in combination with each other: (1) Inhaled mucolytics: rhDNase; (2) nebulised hypertonic saline; and (3) best supportive care (which may include a wide range of inhaled and oral active treatments)".

Both included studies compared mannitol 400mg BD with mannitol 50mg BD. This control, mannitol 50mg, is described by the manufacturer as follows: "*the control arm in both studies was the equivalent of best standard of care on the grounds that mannitol 50 mg should not have any effect in these patients"* (Response to clarification letter, page 13.)

Study 301 included 295 CF patients in total, of these 190 were adults. Study 302 included 305 CF patients in total, of these 151 were adults. An overview of patients included in both studies by subgroups is provided in the table below. Only CF patients listed in the bottom two rows ("Adult rhDNase users" and "Adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase" are relevant for this appraisal.

Table 11: Numbers of patients by intervention and subgroup in study 301 and 302

Study:	**Study 301**			**Study 302**		
Intervention:	**Mannitol**	**Control**	**Total**	**Mannitol**	**Control**	**Total**
Total	177	118	295	184	121	305
Adults	114	76	190	93	58	151
RhDNase users	96	67	163	137	92	229
Adult rhDNase users	58	44	102	64	41	105
Adults ineligible, etc.*	30	13	43	15	7	22

* Adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase

For the first population, adult rhDNase users, both studies provide data for the comparison: mannitol in combination with rhDNase versus rhDNase in combination with best supportive care. For the second population, adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase, both studies provide data for the comparison: mannitol alone versus best supportive care.

No information is provided for the comparison with nebulised hypertonic saline.

Outcomes

The outcomes included in the two studies are described in chapter 4.2.4, above. Although most relevant outcomes were assessed in both trials, very few relevant outcomes for the populations of interest for this appraisal were reported.

2. Mixed treatment comparison

In order to compare mannitol with hypertonic saline, the manufacturer performed a feasibility study to determine whether mannitol could be compared with hypertonic saline via indirect comparison. "Based on this feasibility study, an indirect comparison of Bronchitol and hypertonic saline was not felt to be an appropriate analysis in this situation." (MS, page 82).

In the MS the manufacturer states: "The main limitation of preparing an indirect comparison between Bronchitol and hypertonic saline is the absence of a common control arm between the respective randomised controlled trials. The low dose formulation of Bronchitol (control as used in DPM-CF-301 and DPM-CF-302) may show some degree of clinical activity which would preclude its use as a common link to the hypertonic sale RCTs (control reported to be 0.9% saline (isotonic saline) as in 7/8 studies)." (MS, page 81). However, this is retracted in the response to the clarification letter:

> *Pharmaxis agrees that the argument above was not correctly formulated. Indeed, while low dose of mannitol (40 – 50 mg) may have some degree of clinical activity in children, it has been shown to be sub-therapeutic in adults in the dose-response study (DPM-CF-202) and in both phase III studies.*
>
> *Nevertheless, the main argument for not comparing mannitol to hypertonic saline was not the absence of a common control arm, but rather to significant differences in the design and target population between the mannitol and the hypertonic saline studies.*

COMMENT

There are two main problems with the MS:

1. Very few outcomes have been reported specifically for the two populations of interest for this appraisal; and

2. A comparison with the main active comparator, hypertonic saline, is missing.

The first comparator mentioned in the scope, rhDNase, is no longer a relevant comparator, as all adult CF patients using rhDNase will receive mannitol in combination with rhDNase. Therefore, this intervention can be ignored as a comparator.

Regarding the second comparator mentioned in the scope, hypertonic saline, the ERG feels that as hypertonic saline is mentioned in the NICE scope as the main comparator, the ERG would like to present a comparison based on the best available evidence. However, the limitations of this indirect comparison, as described by the manufacturer (Response to clarification letter, pages 13-15) should be kept in mind

when interpreting the results. See section 4.2.7 for this indirect comparison of mannitol versus hypertonic saline.

4.2.6 Where appropriate, describe and critique any meta-analysis, indirect comparisons and/ or mixed treatment analysis carried out by the manufacturer.

This section should include a summary of the manufacturer's methods and results as described in the MS. The ERG should critique the methods used and interpret the results in light of the methods used by the manufacturer and generalisability to patients in England and Wales.

The meta-analyses in the MS comprised the pooling of data from the two included studies for three outcomes: % predicted FEV1, FEV1 responders and per patient per year rate of protocol defined pulmonary exacerbations (PDPE). These outcomes were considered relevant for the economic model.

None of these analyses included data for the two relevant populations for this appraisal.

Indirect and/or mixed treatment comparisons were deemed inappropriate.

COMMENT

Where possible the ERG has reported data for the relevant populations (see table 7, section 4.2.1). In addition, an indirect comparison of mannitol versus hypertonic saline is reported in section 4.2.7.

When data from the two included RCTs (study 301 and 302) were combined, the ERG pooled the relative effects of each study. In the MS results were combined within each treatment arm and then compared between arms. However, this approach in the MS does not preserve randomisation.

4.2.7 Additional clinical work conducted by the ERG

Provide details of any additional work conducted by the ERG in relation to clinical effectiveness. If the results of any of the additional work affect the size of the ICER, refer the reader to the summary table in Section 6.

In order to do the indirect comparison of mannitol versus hypertonic saline, we will use combined data from the two mannitol studies (301 and 302) and data from Elkins 2006[17]. Where possible data will be presented separately for (1) adult rhDNase users and (2) adults who are ineligible, intolerant, or inadequately responsive to rhDNase.

The study by Elkins et al. (2006) included children 6 years and older and according to table 1 in the paper about 38% (N=164) were regular users of rhDNase. The paper does not report separate data for adults or rhDNase (non)users, but on page 234/235 they say: "The effect of treatment on the linear rate of change

in lung function did not differ significantly according to the baseline FEV1, the use or non-use of rhDNase, age group, or the use or non-use of physiotherapy. The effect of treatment on the absolute level of the FVC and FEV1 during the post-randomization period did not differ significantly according to the baseline FEV1, the use or non-use of rhDNase, or the use or non-use of physiotherapy. The effect of treatment on the absolute level of FVC, but not of FEV1, did differ significantly between adults and children (P = 0.01). For participants who were at least 18 years of age, the absolute level of FVC during the treatment period was 175 ml higher (95 percent confidence interval, 56 to 294; P = 0.004) in the hypertonic-saline group than in the control group, whereas among participants who were younger than 18 years of age, the FVC did not differ significantly between groups (1 ml higher in the control group; 95 percent confidence interval, −72 to 70; P = 0.98)." And on page 235: "The effects of hypertonic saline on exacerbations did not differ significantly between participants who used rhDNase and those who did not use rhDNase."

For the Elkins study we will use data for the full population where no significant differences were found and specific sub-group data where significant differences were found. This should provide the best possible estimate given the paucity of evidence for this comparison.

In their response to the clarification letter the manufacturer describes their concerns regarding an indirect comparison between mannitol and hypertonic saline. With respect to using Elkins at al. for this purpose, they state:

> *The only study that may have been pertinent for indirect comparison was the trial of Elkins et al (c.f., reference 29 of submission dossier). This study included children, adolescents and adults, but only data for the overall population was available. Importantly, this population did not appear to be optimally treated, based on current standard of care. Comparison between the overall population of the Elkins study and the adults from the mannitol studies was not deemed appropriate. Indirect comparison of the overall population from these studies was not feasible either, due to the low beneficial effect of low dose mannitol in children. Furthermore, as shown in the table below, baseline characteristics also differed between studies, particularly in terms of baseline FEV_1 predicted values, proportion of patients with pseudomona aeruginosa infection and antibiotic use. The FEV_1 was higher in the hypertonic saline study and the antibiotic use considerably lower than that reported in the Mannitol studies and current standard care. As presented in Table 1, the effect of hypertonic saline on the rate of PDPE was more pronounced than that of Mannitol (although reduction in incidence was comparable in DPM-CF-301). A direct comparison is not meaningful however in light of the considerably higher proportion of patients on antibiotics in the mannitol studies. The heavy antibiotic medication load in these patients inevitably set a higher hurdle above which additional benefit had to be demonstrated. Despite the low antibiotic use in the Elkins study (approximately 50% of patients), the proportion of patients with pseudomona aeruginosa in suptum at baseline was substantial (78% and 79% of patients in the control and hypertonic saline, respectively). In contrast, mannitol had a higher effect on change of FEV_1 than hypertonic saline despite the higher concomitant medication.*

Table 1. Comparison between the Elkins and the Mannitol studies

	Elkins 2006		DPM-CF-301 (adults)		DPM-CF-302 (adults)	
	HS*[4]	Control	Mannitol	Control	Mannitol	Control
Age (yrs)*[1]	18.4±9.3	18.7±9.2	29.6±9.42	28.8±8.49	24 (18;48)	27 (18;53)
Regular use of antibiotics, n (%)	40 (49.4)	42 (50.6)	167 (94.4)*[3]	105 (89.0)*[3]	140 (76.1)*[3]	97 (80.2)*[3]
Pseudomonas aeruginosa in sputum, n (%)	45 (78)	49 (79)	76 (67)	51 (67)	43 (46)	33 (57)
Baseline FEV_1 (mL)	85.0±18.0	88.0±18.0	58.1±15.91	57.3±16.79	61.9±15.0	59.8±14.3
FEV_1 change from baseline difference*[2]	68.0 [3.0 – 132.0]		105.5 [40.3 – 170.8]		118.5 [10.4 – 226.7]	
PDPE per pat/year	0.39	0.89	1.05	1.43	0.46	0.29

*1 All data are provided as mean (±SD) except for study DPM-CF-302 where data correspond to median (range).
*2 Mean change is from week 26 in the mannitol studies and from week 48 in the Elkins study. Values correspond to mean and ranges.
*3 These values correspond to the overall ITT population (including children and adolescents).
*4 HS: hypertonic saline.

The above arguments precluded an indirect comparison between mannitol and hypertonic saline.

As stated before, rather than completely dismissing the possibility of an indirect comparison between mannitol and hypertonic saline, the ERG decided to present this comparison using the best available evidence.

Regarding the objections mentioned by the manufacturer, the manufacturer claims that "Indirect comparison of the overall population from these studies was not feasible either, due to the low beneficial effect of low dose mannitol in children." In the approach by the ERG, data for the full population were used where Elkins explicitly reported no significant differences for sub-group data. Therefore, this second argument seems less important. Finally the MS states that "baseline characteristics also differed between studies, particularly in terms of baseline FEV_1 predicted values, proportion of patients with pseudomona aeruginosa infection and antibiotic use." This is demonstrated in the table above. Baseline FEV_1 predicted values were indeed higher in the Elkins trial when compared with the mannitol trials, indicating that patients with more severe disease were included in the mannitol trials. There are also differences between trials in scores for proportion of patients with pseudomona aeruginosa infection. However, if the difference between Elkins and DPM-CF-301 (67 % versus 78/79%) makes the studies incomparable; then surely the difference between DPM-CF-301 and DPM-CF-302 (67 % versus 46/57%) would make the two mannitol trials also incomparable. Finally, antibiotic use is indeed considerably higher in the two mannitol trials (78% and 92% versus 50%).

Acknowledging the above mentioned heterogeneity between studies, we will now present the results of an indirect comparison of mannitol versus hypertonic saline based on current best available evidence.

As mentioned before, data from the two included mannitol studies was only reported for the relevant populations for two outcomes: lung function and exacerbations. Elkins et al. reported change in FEV1 and rate of exacerbations for the comparison hypertonic saline versus best supportive care. Results for the

comparisons of mannitol and hypertonic saline versus best supportive care and for the indirect comparison of mannitol versus hypertonic saline are reported in table 12.

Table 12. Indirect comparison of mannitol versus hypertonic saline

Outcome	Mannitol vs BSC	HS vs BSC	Mannitol vs HS
(1) Adult rhDNase users			
Change in FEV1 (mL)	MD = 91.77 (30.85, 152.69)	MD = 68 (95% CI: 3, 132)	23.77 (-64.95, 112.49)
Exacerbations (incidence)	RR = 1.00 (0.61, 1.66)	NR	
Exacerbations (rate ratio)	Rate Ratio=1.14 (0.75, 1.73)	NR	
Exacerbations (mean)*	NR	MD = -0.5 (-0.86, -0.14)	
(2) Adults who are intolerant/non-responsive to rhDNase			
Change in FEV1 (mL)	MD = 162.32 (51.77, 272.87)	MD = 68 (95% CI: 3, 132)	94.32 (-33.67, 222.31)
Exacerbations (incidence)	RR = 0.44 (0.18, 1.10)	NR	
Exacerbations (rate ratio)	Rate Ratio=0.50 (0.18, 1.40)	NR	
Exacerbations (mean)*	NR	MD = -0.5 (-0.86, -0.14)	

*=mean number of exacerbations per participant;
BSC=Best Supportive Care; HS=Hypertonic Saline; RR=Relative Risk; MD=Mean Difference; CI=Confidence interval

As can be seen in table 12, mannitol is superior to hypertonic saline in terms of change in FEV1 in adult rhDNase users (MD = 23.77 (-64.95, 112.49)), although the difference is not statistically significant. In adults who are ineligible, intolerant, or inadequately responsive to rhDNase, there is no significant difference between mannitol and hypertonic saline in terms of change in FEV1 (MD = 94.32 (-33.67, 222.31)). In terms of exacerbations, hypertonic saline seems superior; although, an indirect comparison is not possible because different outcomes are reported for the different studies. In studies 301 and 302 exacerbation rates are reported (defined as the number of exacerbations divided by the number of participant-years of follow-up), while Elkins et al. reported the mean number of exacerbations per patients. Nevertheless, in rhDNase users the rate of exacerbations was worse for mannitol when compared with best supportive care, while hypertonic saline was significantly better than best supportive care for the number of exacerbations per patient; suggesting that hypertonic saline probably will result in fewer exacerbations than mannitol. For the adults who are ineligible, intolerant, or inadequately responsive to rhDNase the results are likely to be more similar.

As mentioned before, these data have to be interpreted with great caution. Not only because of the heterogeneity between studies, but also because of the uncertainty of the data. Data for 'changes in FEV1' were provided by the manufacturer in the response to the clarification letter. However, these data were presented as graphs; therefore, the confidence intervals had to be estimated from the pictures. Nevertheless, these are the best data available to the ERG at this moment.

4.3 Conclusions

Describe the completeness of the MS with regard to relevant clinical studies and relevant data within those studies. Does the submission contain an unbiased estimate of the technology's (relative and absolute) treatment effects in relation to relevant populations, interventions, comparators and outcomes? Are there any remaining uncertainties about the reliability of the clinical effectiveness evidence? Reference should also be made concerning the extent to which the submitted evidence reflects the decision problem defined in the final scope.

The NICE scope for this appraisal was to assess the clinical effectiveness and cost effectiveness of mannitol dry powder for inhalation, alone or in combination with rhDNase, compared with inhaled mucolytics (rhDNase), nebulised hypertonic saline, or best supportive care in people with cystic fibrosis.

However, according to the industry submission the expected license indication for mannitol is for: *"treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to rhDNase, and in adults ineligible, intolerant, or inadequately responsive to rhDNase".*

This means that the population, intervention and comparators have changed from the original scope. After discussion with NICE it was agreed that there are now two distinct interventions for two separate populations: (1) Mannitol in combination with rhDNase for adults with cystic fibrosis, and (2) Mannitol alone for adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase. Regarding comparators, it was agreed that rhDNase is no longer a relevant comparator.

The industry submission provides evidence from two RCTs comparing mannitol 400mg with mannitol 50mg over 26 weeks in people with CF, aged >= 6 years (studies 301 and 302). According to the manufacturer "*the control arm in both studies was the equivalent of best standard of care on the grounds that mannitol 50 mg should not have any effect in these patients".* Data from both trials are publicly available as conference abstracts only. Data from these two trials would allow for a comparison of mannitol with best supportive care in both populations (adult rhDNase users and adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase). However, in the MS only lung function is reported for one of the relevant populations for this appraisal: adult rhDNase users. In response to the clarification letter, the ERG received data for both populations, adult rhDNase users and adults who are ineligible, intolerant, or inadequately responsive to rhDNase, for change in FEV1 (graphs only) and exacerbations. No other data were provided, despite our request for all relevant data for the relevant populations. Results show that in adult rhDNase users, there are no significant differences in exacerbations between mannitol and best supportive care (incidence: RR=1.00 (95% CI: 0.61, 1.66); rate per year: MD=0.42 (95% CI: -0.12, 0.97)); but mannitol leads to a significant improvement in change in FEV1 (MD=91.77 (95% CI: 30.85, 152.69)) when compared with best supportive care. In adults who are ineligible, intolerant or inadequately responsive to rhDNase, there are no significant differences in exacerbations between mannitol and best supportive care (incidence: RR=0.44 (95% CI: 0.18, 1.10); rate per year: MD=-0.37 (95% CI: -0.90, 0.16)); while mannitol leads to a significant improvement in change in FEV1 (MD=162.32 (95% CI: 51.77, 272.87)) when compared with best supportive care.

In order to compare mannitol with hypertonic saline, the manufacturer performed a feasibility study to determine whether mannitol could be compared with hypertonic saline via indirect comparison. "Based on

this feasibility study, an indirect comparison of Bronchitol and hypertonic saline was not felt to be an appropriate analysis in this situation."

The ERG agrees with most objections of the manufacturer regarding heterogeneity between studies. Nevertheless, given the fact that hypertonic saline was mentioned explicitly in the NICE scope, the ERG would like to present the results of an indirect comparison based on current best available evidence. However, it should also be stressed that some data had to be guessed from graphs, making the analyses even more unreliable.

Results of the indirect comparison showed that mannitol is superior to hypertonic saline in terms of change in FEV1 in adult rhDNase users (MD = 23.77 (-64.95, 112.49)), although the difference is not statistically significant. In adults who are ineligible, intolerant, or inadequately responsive to rhDNase, there is no significant difference between mannitol and hypertonic saline in terms of change in FEV1 (MD = 94.32 (-33.67, 222.31)). In terms of exacerbations, hypertonic saline seems superior in adult rhDNase users; although, an indirect comparison is not possible because different outcomes are reported for the different studies.

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 State objective of cost effectiveness review. Provide description of manufacturers search strategy and comment on whether the search strategy was appropriate. If the manufacturer did not perform a systematic review, was this appropriate?

The objective of the cost effectiveness review in the MS was to identify any existing cost-effectiveness studies in the field of CF. Studies were identified from the published literature by searching PubMed and CRD databases. The search identified 10 relevant items. No items carry out cost effectiveness studies on mannitol.

The search strategies for the cost-effectiveness review are discussed in detail in section 4.1.1.4.

5.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The MS did not include any statement on the in- and exclusion criteria in the study selection for the cost effectiveness review.

COMMENT

The ERG cannot comment on the in- and exclusion criteria as they were not described in the MS.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the most important cost effectiveness studies.

The manufacturer's submission identified ten cost-effectiveness studies. While the quality of the studies was assessed, this was done using four possible scores per item (Yes, No, Not Applicable, Not Clear), without any further discussion.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

No specific conclusions from the economic review were provided in the MS.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

Summarise and critique the cost effectiveness evidence submitted by the manufacturer (headings 5.2.1 to 5.2.11 are suggested headings). It is noted that the ERGs may prefer NOT to combine the summary and critique of the submitted economic evidence and instead report summary and critique sections separately.

An overall summary of the *de novo* economic model developed by the manufacturer is given in Table 13.

Table 13: Summary of the manufacturer's economic evaluation Mannitol for cystic fibrosis (with signposts to MS)

	Approach	Source / Justification	Signpost (location in MS)
Model	Individual patient simulation model based on a Markov health state transition model. Cycle lengths are 6 for 1st cycle, 8 for 2nd, and 12 weeks subsequently. Time horizon was life expectancy.	Patient characteristics are memorised and influence individual state transitions and events such as exacerbation rate. Cycle lengths are based on the follow-up periods in the trial data i.e. 1st 6, next 8 and final 12, making 26 in total.	From pg. 118
States and events	Health states: CF; CF improved respiratory symptoms on 1st line treatment; CF switched to 2nd line treatment; CF improved RS on 2nd line treatment; lung transplantation; death due to CF; death to other cause. In case FEV1≤30% a patient is eligible for lung transplantation. No response to Mannitol leads to switch to 2nd line treatment. Exacerbations might be experienced during a cycle. This increases the risk of a subsequent exacerbation, being eligible for lung transplantation and the risk of dying due to CF		From pg. 122
Comparators	Population of adult rhDNase-users: Mannitol+rhDNase (with rhDnase+BSC in case of non-response) vs. rhDNase+BSC Population of adults ineligible, intolerant, or inadequately responsive to rhDNase : Mannitol (with BSC in case of non-response) vs. BSC	Scope as specified by NICE. Upon request of the ERG, cost-effectiveness is assessed separately for the two populations	Pg. 119
Natural History	Disease progression is captured by the individual patients decline in lung function. Acute worsening of lung function is captured as pulmonary exacerbation.	Individual patient data for the 1st 26 weeks and registry data from BioGrid Australia Ltd.[44]	From pg. 123
Treatment effectiveness	Yes/no improvement in respiratory symptoms) was determined by CFQ-R ≥4 improvement. This is considered to be of minimally clinical importance.		Pg. 122

	Also, effect treatment on FEV1 % predicted and exacerbation rate.		
Adverse events	Adverse events of mannitol were considered not to substantially impact costs or quality of life and were not included in the analysis.	No specific justifications were given.	Pg. 124-125
Health related QoL	Health related quality of life is expressed in QALYs based on HUI. Average changes in utility from average baseline values were determined for each Markov state. Exacerbations had impact expressed in utility decline. Post lung transplant utilities were determined	Baseline and 14 week change in HUI were measured in the pivotal trial DMP-CF302. The impact of exacerbation on utility was derived from a conference abstract from Bradley 2010.[45] Post lung transplant utility was taken from Anyanwu.[46]	Pg. 147 and 153
Resource utilisation and costs	Markov state costs (total 6 monthly costs treated with Mannitol, or treated with control) were determined for the treatment options. No distinction was made according to respiratory improvement. Markov state transition costs were related to exacerbation and lung transplantation. Post transplant costs were Markov state specific.	Resource use was derived from both pivotal trials using medical dossiers and patient diaries. Prices were taken from National reference costs. Costs of exacerbation were based on the trial findings. Costs for lung transplant and post lung transplant period were taken from UK specific literature.	From pg. 168
Discount rates	A 3.5% discount rate was used for both costs and utilities	According to NICE reference case	Pg. 125
Sub groups	Subgroup analyses were performed according to lung function (FEV1>80; 60-79; 40-59; <40) and mannitol responders only.	No specific justifications were given.	Pg. 26 and 193
Sensitivity analysis	One-way sensitivity analyses are provided for all major model variables in order to identify model drivers. Probabilistic sensitivity analysis was also undertaken.	Ranges and distribution for most parameter distributions were based on confidence intervals and empirical data.	From pg. 173

The ERG has assessed the manufacturer's economic evaluation using the Philips et al. checklist for quality assessing decision analytic models.[47] This is shown in Appendix 3 and is used to assist the narrative critique in the following sections.

5.2.1 NICE reference case checklist

Table 14: Comparison of the MS model with the NICE reference case

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes	
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	Model has time horizon of 100 years: at that moment all patients have died.
Synthesis of evidence on outcomes	Systematic review	No	For most model parameters findings from two pivotal trials were used

5.2.2 Model structure

The model that was developed for the current economic evaluation is a patient-level simulation Markov model which means that the progression of each individual patient is modelled, rather than the progression of a whole patient cohort at once. As patients move through the model one at a time the model memorises specific patient characteristics like lung function, age, and body mass index (BMI), which are updated over time. These characteristics are taken into account when determining the transition probabilities and thus the path through the tree. A schematic presentation of the relationship between treatment, time, clinical endpoints and economic endpoints is shown in Figure 1.

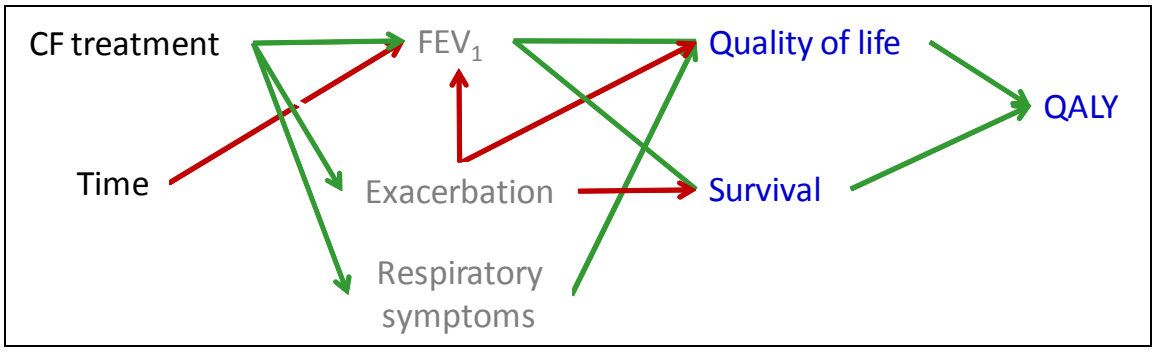

Figure 1 Schematic presentation of the relationship between treatment (black), time (black), clinical endpoints (grey), and model endpoints (blue).

A green arrow indicates a positive relationship and a red arrow indicates a negative relationship between factors.

A graphic presentation of the model structure is presented in Figure 2 and Figure 3.

The following health states can be distinguished in the model:

- Cystic fibrosis
- CF with improved respiratory symptoms
- Lung transplant
- Death due to CF
- Death due to unrelated cause

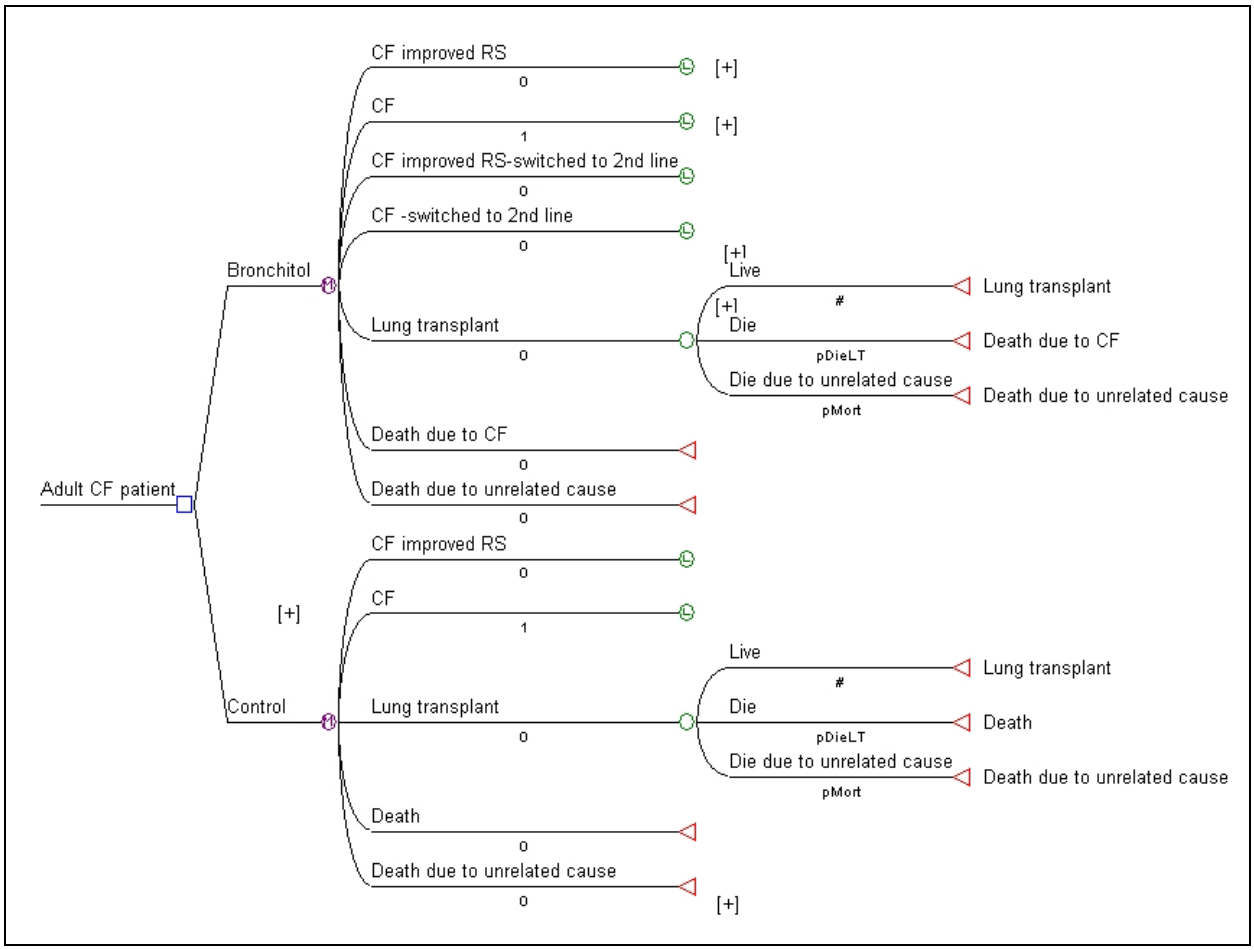

Figure 2 Core structure of the economic model

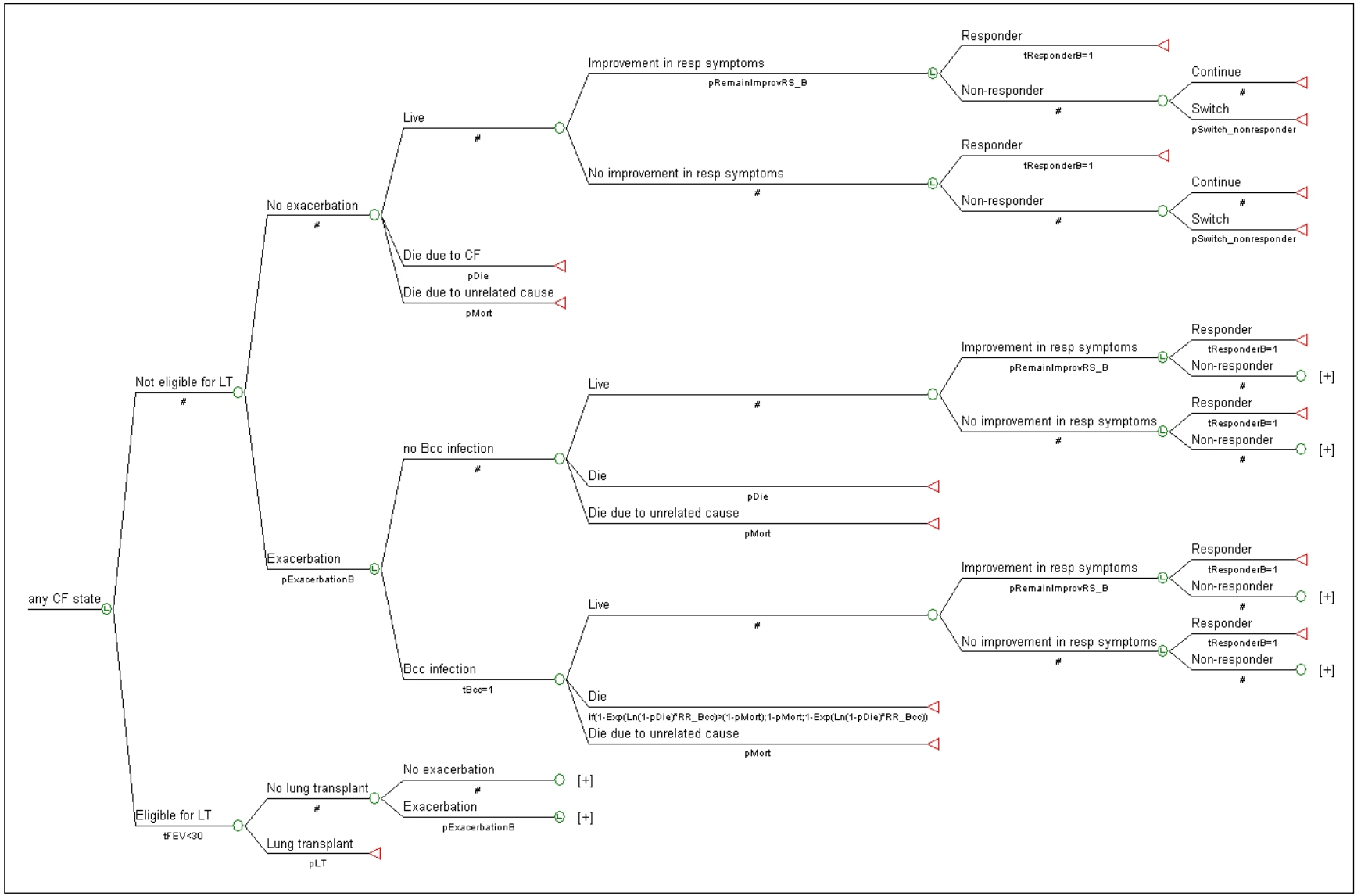

Figure 3 Structure for any CF health state

The Control treatment arm from study DPM-CF-301 and DPM-CF-302 is assumed to represent standard care in the real-life setting.

The model assesses the cost-effectiveness of two distinct strategies for the treatment of CF in adults aged 18 years and above: as an add-on therapy to rhDNase, and as second line treatment in patients ineligible, intolerant, or inadequately responsive to rhDNase. For the first strategy, mannitol + rhDNase is compared to standard treatment + rhDNase. For the latter strategy, mannitol is compared to standard treatment (best supportive care).

Patients move through the model as follows: all patients start in 'Cystic Fibrosis' and based on their lung function measured by FEV1 they either continue treatment (FEV1≥30%), or they are eligible for a lung transplant (FEV1 <30%). This cut-off is based on the treatment guidelines for a lung transplant in CF patients. Note that patients eligible for lung transplantation follow the same path as those not eligible up until the moment of transplantation.

Patients not responding to mannitol treatment in the first cycle (6 weeks) will stop mannitol treatment and switch to standard therapy. Response was defined as a relative increase of at least 5% or an absolute increase of at least 100ml in the FEV1 at week 6 from baseline.

During the second cycle (8 weeks, i.e. between 6 and 14 weeks since start model) a patient may experience improvement in respiratory symptoms (≥4 points improvement in the CFQ-R respiratory domain score). During the next 12-week cycles, patients that improved could move back to the CF health state, and patients who showed no improvement in the last cycle may show an improvement in the next cycle.

Both in the 'CF' and the 'CF improved RS' health state, CF patients may experience pulmonary exacerbations. The rate of pulmonary exacerbations depends upon the patient's age, the history of exacerbations in the previous year and whether the patient is receiving Mannitol or standard therapy.

During each cycle, the model updates the patients age, BMI and FEV1. BMI is assumed to increase until the age of 40 (men 0.19 per year, women 0.1 per year). FEV1 at 26 weeks is predicted using a regression model, including treatment group, BMI at baseline, FEV1 at 6 weeks, respiratory symptoms and responder/non-responder as covariates. For all subsequent cycles, FEV1 declines with age (1.02% per year until the age of 30, after that an increase by 0.64% per year) and with exacerbations (2.08% decrease if an exacerbation occurred in the previous cycle).

During each cycle the patient has the chance to die due to CF or to unrelated cause. By default the probability of dying is based on the lung function and age. However this probability is elevated when the patient has an exacerbation in combination with a Bcc (Burkholderia cepacia complex) infection. In addition, when a patient received a lung transplant the probability of dying is equal to the annual death rate among transplanted patients with cystic fibrosis, irrespective of lung function and age.

For the first 26 weeks, input for the economic model is derived from an analysis of individual patient level data from the two main clinical studies. From here the model extrapolates to a lifetime horizon based on observational data from an Australian database (BioGrid),[44] supplemented with literature data.

COMMENT

The Markov states and transitions defined in the model describe more the clinical studies with Mannitol than the natural disease course of cystic fibrosis. In general, relative health states (such as improved respiratory symptoms) should be avoided. However, since the Markov model was used for individual patient simulation, with transitions, events, and utilities dependent on the individual's absolute FEV1 % predicted, the ERG considers the current model structure appropriate for the research question.

5.2.3 Population

In the scope document for mannitol in cystic fibrosis there is no further specification of the population. The scope acknowledges the fact that mannitol is being studied alone and in combination with rhDNase, in clinical trials including CF patients aged 6 years and older.

In the manufacturer's submission it is stated that the economic evaluation is based on the pooled data from the pivotal studies DMP-CF- 301 and DMP-CF-302. In line with the expected licensed indication only the data of adult patients (aged 18 or above) from these 2 trials have been included in the economic evaluation. The statement was made that different scenarios will be performed in addition to this base case analysis for the entire population (age >6 yrs) as well as different age groups (page 25, MS).

It should be noted that in the original MS, pooled analyses on all rhDNase users and rhDNase non-users in the overall population were presented; in addition results were reported for adult CF patients. However, results were not reported separately for adult rhDNase users and adult rhDNase non-users. In the response to the clarification letter, the manufacturer provided data for adult rhDNase users and adult CF patients who are ineligible, intolerant or inadequately responsive to rhDNase separately (see also Figure 4).

In the original model submitted by the manufacturer, even though separate analyses were done for mannitol + BSC and mannitol + rhDNase, all analysis were done on data from the whole adult population, regardless of their rhDNase status. The differences between the two mannitol strategies were solely on the cost side of the cost-effectiveness analysis.

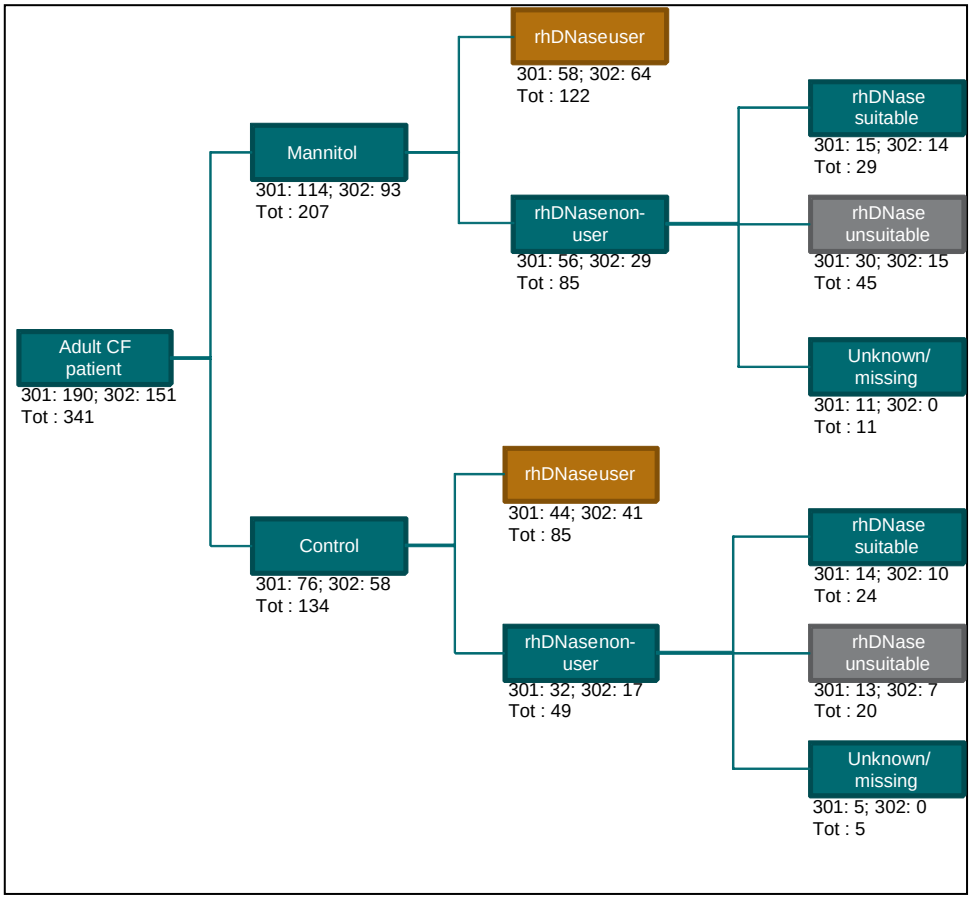

Figure 4 Proportion of adults ineligible, intolerant or inadequate responsive to rhDNase in the pivotal studies (original figure taken from manufacturers Response to Clarification Questions)

COMMENT

The ERG was not able to find or perform scenario analyses for patient populations other than adults only, although it was mentioned in section 4 of the MS (page 25) that different age groups will be modelled as a separate scenario.

Furthermore, the ERG considers the patients defined as unsuitable for rhDNase in the response to the clarification questions to be the patients that are ineligible, intolerant or inadequate responsive to rhDNase. The total group of non-users does not fit the scope since this group contains patients that are suitable for rhDNase treatment but presumably their CF-status does not indicate being treated by this drug yet. Therefore, given that the cost-effectiveness evidence reported that is based on the total group of non-

users is not suited in the context of the scope, the focus will be on rhDNase-users on the one hand, and rhDNase unsuitable patients on the other hand.

5.2.4 Interventions and comparators

The *de novo* model developed for this submission included the following treatment options:

- Best supportive care (BSC) consisting of multiple medications and drug therapy. These often include inhaled antibiotics, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes and antidiabetic agents for patients with diabetes. The control treatment arm from studies DPM-CF-301 and DPM-CF-302 are considered to represent best supportive care (standard care) in the real-life setting.
- rhDNase reduces the viscoelasticity of airway secretions by catalysing the hydrolytic cleavage of phosphodiester linkages in the DNA backbone. RhDNase is an effective mucolytic but has not been shown to increase mucociliary clearance.
- Mannitol (mannitol dry powder for inhalation) is a non-ionic osmotic, mucolytic agent that acts by inducing an influx of water into the airway lumen improving hydration of airway secretions, and increasing mucociliary clearance by reducing its viscosity and stimulating cough. Mannitol dry power is administered by inhalation with a hand-held, breath activated device and is encapsulated in a size 3 hard gelatine capsules as 40 mg of spray-dried mannitol powder for inhalation. The recommended dose is 400 mg mannitol (10 capsules of 40 mg), twice a day. In the trials DPM-CF-301 and DPM-CF-302 mannitol 50 mg dose was used in the control arm, however according to the manufacturer the data show that this low dose is sub-therapeutic in the adult population.

Upon initiation with mannitol, patients are placed on a trial for a period of 6 weeks. At the end of the trial period FEV1 improvement is used to assess whether the patient has responded. Patients achieving at least 5% relative improvement in FEV1 or an absolute improvement of >=100 ml in FEV1 after 6 weeks of treatment continue mannitol treatment; all other patients discontinue mannitol treatment after the 6-week period.

Mannitol is indicated for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to rhDNase, and in patients ineligible, intolerant, or inadequately responsive to rhDNase. Mannitol was trialled on top of these standard therapies and there were limited restrictions on the co-medications or treatment provided in the study. The Control treatment arm from study DPM-CF-301 and DPM-CF-302 represents standard care in the real-life setting

Two comparisons are made in the economic model. First, for the population of adult rhDNase-users, the comparison is made Mannitol+rhDNase (followed by rhDnase+BSC in case of non-respons) vs.

immediate rhDNase+BSC. Secondly, for the population of adults ineligible, intolerant, or inadequately responsive to rhDNase the comparison is made mannitol with BSC (followed by BSC in case of non-respons) vs. immediate BSC.

COMMENT

Current CF patient management involves the use of multiple therapies such as bronchodilators, steroids, physiotherapy, antibiotics, hypertonic saline and rhDNase. However, as becomes clear from the manufacturers description of best supportive care, only bronchodilators, steroids, physiotherapy and antibiotics can be regarded to be part of this treatment mix, which fits with the scoping document that stated that hypertonic saline and rhDNase were considered relevant comparators to mannitol.

However, hypertonic saline did not form a comparator in the manufacturer's submission. This was motivated by the opinion that usage in UK centres is limited to the range of only 10-30% of CF patients, the dosages used are often below the 7% strength used in the only long term study, and also the frequency of dosage is normally once a day rather than the twice a day. Also, as no study has directly compared mannitol to hypertonic saline an assessment has to rely on indirect comparison. For this purpose, a literature search was carried out by the manufacturer to identify studies which would potentially be relevant for an indirect comparison. Ten studies (mannitol vs. control n=2, hypertonic saline vs. control: n=8) were included for further consideration. The main limitation of preparing an indirect comparison were the absence of a common control arm between the respective randomised controlled trials and the idea that there were differences in inclusion/exclusion criteria and baseline study characteristics between trials. Based on this literature study, an indirect comparison of mannitol and hypertonic saline was not felt to be an appropriate analysis in this situation. This was illustrated by comparing the baseline patient characteristics of the Elkins study[17] on hypertonic saline and the mannitol trials. Due to significant differences in the design and population between the mannitol and this one hypertonic saline study the manufacturer concluded that is not feasible to compare mannitol to hypertonic saline.

In the clarification letter, the ERG noted that the submission did not assess the cost-effectiveness of mannitol compared with hypertonic saline as outlined in the scope and that an attempt should have been made to do so. The manufacturer did not follow this request. In addition to the submission, in the answers to the clarification the manufacturer states that mannitol will not replace hypertonic saline when hypertonic saline is effective and well tolerated in the individual. Based on data from a European survey amongst CF physicians in 5 European countries, it was concluded that the low use of hypertonic saline among patients with cystic fibrosis also highlights that it would be an inappropriate comparator to

mannitol. The perceived role of hypertonic saline would appear to be different to that of rhDNase or mannitol as hypertonic saline is being used as an aid to physiotherapy so in fact in a population with less severe CF. Treatment with rhDNase was primarily initiated because of severity of lung disease and rate of lung function decline, whereas the primary reason for initiation of hypertonic saline was to aid physiotherapy. In line with this, an expert panel were interviewed following an introduction to the clinical data of mannitol. They stated that mannitol was most likely to be prescribed to patients with more severe lung disease – i.e.: a similar patient group to those who were utilising rhDNase. In fact, the manufacturer considers that the comparator hypertonic saline as defined in the scope was irrelevant.

While the ERG agrees that there is heterogeneity between studies; especially regarding baseline antibiotics use and baseline FEV1 (see also section 4.2.7), given the fact that hypertonic saline is explicitly mentioned in the NICE scope it is important to provide an indirect comparison based on the best available evidence taking the heterogeneity between studies into account when interpreting the results. Based on the indirect comparison of mannitol and hypertonic saline as described in section 4.2.7, the ERG will attempt to calculate the cost-effectiveness of this comparison.

5.2.5 Perspective, time horizon and discounting

The manufacturer's model applied a life expectancy time horizon (maximum 100 years). The cycle length is variable: 6 weeks in the first cycle, 8 weeks in the second cycle and 12 weeks in all subsequent cycles. The motivation for this variation is that the first two cycles represent clinical practice best: after 6 weeks response to mannitol is determined and a switch to BSC made in case of inadequate response. In the trials at 14 weeks the patients situation was assessed, which motivates the length of the second cycle. The 12 weeks cycle length is based on the 26 weeks follow up visit in the trials which was continued in the subsequent cycles.

The discount rates applied was 3.5% for utilities and costs and costs are considered from an NHS and Personal Social Services perspective

COMMENT

The ERG concludes that the discount rates and perspective are in line with the NICE reference case. The life expectancy time horizon is relevant given this is a chronic disease.

5.2.6 Treatment effectiveness

The transitions in the model can be divided into those that are treatment independent and those that are treatment dependent. We will first discuss the treatment independent set of parameters and then the treatment dependent set.

5.2.6.1 Treatment independent parameters

Baseline patient characteristics

The baseline patient characteristics from the pooled trial adult population were used in the model.

Table 15 Baseline patient characteristics

Parameter	Mannitol	Control	Total
N	207	134	341
Gender (% male)	61%	53%	58%
Age (years)	28.3	28.8	28.5
BMI (kg/m^2)	22.6	22.1	22.4
FEV1 % predicted	59.9	58.4	59.3

Natural decline FEV1 % predicted

The rate of lung function decline in CF patients over time was estimated using Australian observational data.[44] A repeated measures mixed model analysis was undertaken to estimate the mean rate of decline of FEV1 % predicted over time as a function of covariates such as age, gender, BMI and of inpatient hospital admission days per quarter. To this end, for each patient in the database and in each calendar quarter, the highest measured FEV1 % predicted was recorded. The covariance structure resulting from the repeated measures mixed model was used in the Cholesky decomposition technique to provide correlated draws from a multivariate normal distribution for the probabilistic sensitivity analysis.

The final model results are presented below (Table 67 and appendix 16 in the MS).

Table 16 Mixed model estimate of rate of lung function decline (Adults only)

	Solution for Fixed Effects				
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	85.5864	4.4401	391	19.28	<.0001
age	-1.0174	0.1975	368	-5.15	<.0001
age_plus30	1.6536	0.4575	247	3.61	0.0004
hosp_days/qtr > 0 (baseline=0)	-2.0787	0.5581	270	-3.72	0.0002

The model shows that lung function decreases on average by 1.02% per year to the age of 30 after which it tends to increase slightly by 0.64% per year. However hospitalisation during the same quarter is associated with a 2.08% decrease in lung function. In the MS (page 137), possible reasons for the observed increase beyond the age of 30 years are suggested, such as:

1) there were fewer data beyond the age 30 years;
2) potential survival bias;
3) as older patients are more likely to be hospitalised, some of the apparent improvement will be offset by decreases in lung function associated with hospitalisation.

In the model, this equation is used to update a patient's FEV1 % predicted in each cycle. The covariate 'hospitalisation in the same quarter' has been translated into 'exacerbation in the previous cycle' in the model.

Probability of severe exacerbation in CF population

The same Australian observational data used for the lung function decline was also used to estimate the probability of a severe exacerbation. However, since there was a lack of information on exacerbations in that database, the number of inpatient hospital admissions per quarter was used as a proxy for the rate of severe exacerbations. The data are presented below (see also MS table 68).

Table 17 Hospitalisation rate

Patient population	Hospital Days/Quarter				#PTS with hospital days:			
	0		>0		0	>0	All	
	#quarters	%	#quarters	%	N	N	N	Rate
Adults	5,669	72%	2,202	28%	1,634	1,170	2,804	0.785
Adults<=30 years	3,979	75%	1,344	25%	1,190	729	1,919	0.700
Adults>30 years	1,690	66%	858	34%	444	441	885	0.969

Source: BioGrid Australia 2011[48]

The exacerbation rate was calculated for each patient group as the number of quarters with at least 1 hospital day divided by the total number of patients. Thus, the exacerbation rate for patients under the age of 30 years is 1344/1919 = 0.7 per year. This rate is used in the model as long as the patient is aged 30 or under. For patients above the age of 30, this was corrected by applying a relative risk of 1.38 (0.969/0.700) to the baseline risk.

Additionally, the exacerbation rate was adjusted for patients with an exacerbation in the previous year based on the observed elevated risk of exacerbation for patients with exacerbations in the year preceding the participation in the DPM-CF-302 study (RR=1.59, p<0.001).

Probability of lung transplantation

In the model a patient is eligible for a lung transplant if the FEV1 percent predicted <30%, which was based on the treatment guidelines for a lung transplant in CF patients. For eligible patients, the probability to receive a lung transplant is based on the UK CF Registry Annual Data Report 2008.[49] Of those with complete data in 2008, 126 patients had been evaluated and 55 accepted onto the transplant list. 24 received transplants (i.e. a probability of 0.19).

CF Mortality

Cystic fibrosis patients have lower life expectancy than the general community. Survival has been linked to lung function and a number of factors including BMI and specific respiratory infections. Data from the Australian observational study[44] was used to investigate CF mortality and explore predictors. Based on the observed data, age and gender specific life tables were generated, giving CF mortality for the average CF population. Next, a Cox's proportional hazard survival model was developed. Since FEV1 % predicted was the primary outcome of the mannitol pivotal trials particular focus was on the relationship between FEV1 % predicted and survival. Other potential risk factors, like gender and BMI were also investigated. In the MS the following table was presented (table 69 in MS). In the manuscript it was remarked that FEV1 % predicted and BMI were included as time varying covariates in the model.

Table 18 Analysis of CF survival. Model with FEV1 and BMI

Analysis of Maximum Likelihood Estimates						
Variable	**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**
ppFEV1	1	-0.04376	0.00736	35.3898	<.0001	0.957
Bmi	1	-0.06900	0.04486	2.3651	0.1241	0.933

Source: BioGrid Australia 2010

However, in the electronic model only the FEV1 % predicted was used as a covariate. At the ERG's request in the clarification letter, the manufacturer provided the correct parameter estimate for the regression model with only FEV1 % predicted as covariate. In the ERG defined base case analysis, the above hazard rate has been used (see also section 6)

Table 19. Analysis of CF survival. Model with FEV1

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
ppFEV1	1	-0.04879	0.00671	52.8923	<.0001	0.952

In the response to the clarification letter, the manufacturer also showed how the above hazard ratio is translated into a patient-specific probability of dying:

For male patients: pDie = 1-Exp(-Mortality_CF[tAge;male]*0.952^(FEV1-58.57)*_CycleLength)

For female patients: pDie = 1-Exp(-Mortality_CF[tAge;female]*0.952^(FEV1-61.48)*_CycleLength)

In words, the probability to die in the model is calculated using the life table method (depending on the age and gender of the patient) corrected for the hazard ratio for FEV1 % predicted based on the difference of a patient's FEV1 % predicted at a certain time point from the overall mean FEV1 % predicted observed in the BioGrid patient sample. Note that the yearly mortality rate is adjusted for cycle length.

The manufacturer also performed a literature search in order to compare the Australian analysis results with previously published studies. They identified six studies which provided an estimate of the relationship between FEV1 and survival. In each study FEV1 was expressed as % predicted. Estimates were remarkably consistent across time and for both multivariate and univariate analyses. Only Ellaffi et al. did not show a link between FEV1 and survival, however, this study was of older hospitalised patients with very low FEV1 (28% predicted).[50] The literature review presented in table 70 of the manufacturer's submission provides strong evidence that a 1% improvement in FEV1 is related to approximately 5% reduction in mortality.

Excess mortality due to exacerbation and Bcc infection

Using the same literature review as above, a number of other potential risk factors were identified (e.g., BMI, malnutrition, liver complications, Pseudomonas aeruginosa (Pa) infection, Bcc infection). However, based on the clinical trials, none of these were expected to be changed by mannitol treatment. The only factor that is changed by mannitol is the combination of a pulmonary exacerbation and a Bcc infection. A review of the literature for evidence of the effect of exacerbation rates on mortality found that the

combination of having a Bcc infection when having an exacerbation was found to be a strong predictor of mortality. The chance of dying increased by a factor 3.41 (95% CI 1.08 – 10.75) compared to those without a Bcc infection.[50] Thus, in the model, a relative risk of 3.41 is applied to the CF mortality rate in patients experiencing an exacerbation who also have a Bcc infection. However, patients experiencing an exacerbation who have no Bcc infection do not have an increased mortality compared to patients without an exacerbation.

Transplantation mortality

Mortality for patients who received a lung transplant were based 10-year survival data from UK patients receiving a lung transplant between 1995-1997 (see table 66 in MS).[51]

Table 20 Transplant mortality

Time since LT (years)	Yearly Mortality rate (rLT)	Percentage	n	N
1	0.357	30%	90	300
2	0.121	11%	24	210
5	0.122	31%	57	186
10	0.108	42%	54	129

Non-CF mortality

The all cause mortality rate was estimated from UK life tables from the UK Actuaries Department, based upon the gender distribution from the trial and age specific.

5.2.6.2 Treatment dependent parameters

Effect of treatment on FEV1 % predicted

Improved lung function is incorporated in the cost-effectiveness analysis as a one-time increase in FEV1 % predicted during the first 6 months. A linear regression analysis was performed to obtain a prediction of the FEV1 % predicted at the end of the trial follow-up period, i.e. week 26. The final model is presented in the table below (see table 55 in MS). The covariance structure resulting from the regression model was used in the Cholesky decomposition technique to provide correlated draws from a multivariate normal distribution for the probabilistic sensitivity analysis.

Table 21 Linear regression model for FEV1 % predicted at week 26 (Adults only)

Variable	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	-7.76767	3.19289	-2.43	0.0156
Treatment group	1.52254	0.84022	1.81	0.0710
BMI at baseline	0.36902	0.12207	3.02	0.0027
FEV1 % predicted at baseline	0.93357	0.02715	34.38	<.0001
PDPE during DBP	-2.15803	1.00012	-2.16	0.0318
Responder	6.63425	0.83526	7.94	<.0001

The clinical trials both provided treatment periods of only 26 weeks. Mannitol is intended for lifetime use and so the results of the trials need to be extrapolated over the life time of a patient. The manufacturer made the assumption that the benefit in lung function achieved in the first six months will be maintained over the patient's lifetime, assuming that he/she will receive therapy (responders at 6 weeks only) for the remainder of his life.

The model presented above does not distinguish between patients receiving mannitol as add-on therapy and those receiving mannitol as second line therapy. Thus, the ERG requested information on the effect of treatment on FEV1 % predicted in both subgroups. In their response, the manufacturer presents the results separately for rhDNase users (add-on treatment) and rhDNase non-user unsuitable (second line treatment).

Table 22. Linear regression model results for FEV1 % predicted at week 26 per subgroup

Variable	**All adults (N=341)**	**rhDNase user (N=207)**	**rhDNase non-user (N=134)**	**rhDNase non-user unsuitable (N=65)**
Intercept	-7.97	0.38	-4.23	-9.61
Treatment group	1.81	2.54	0.19	4.08
FEV_1 % predicted at baseline	0.93	0.94	0.91	0.83
Responder	5.23	4.55	6.07	5.43
BMI at baseline	0.38	NS	0.44	0.70
Improvement in resp symptoms	1.73	NS	NS	NS
Sa infection	NS	NS	-2.70	NS
Number of PDPEs	NS	NS	-2.83	NS

NS: Not statistically significant

Effect of treatment on pulmonary exacerbations

In the section on treatment independent parameters, the baseline exacerbation rate was discussed. Treatment with mannitol influences this exacerbation rate. In the MS the rate ratio of having a PDPE for patients who respond to mannitol was calculated by the observed difference in PDPE rate in patients who responded to mannitol compared to the overall PDPE rate in the Control group. The values used to calculate the rate ratio (RR=0.65) in the economic evaluation are presented in table 23 below (

Table 56 in MS) (Note that the MS uses the term 'relative risk' instead of the correct term 'rate ratio').

Table 23 PDPE rates from combined DMP-CF-301 and DMP-CF-302 (Adults only)

	Control			Mannitol	
	Non-responder	**Responder**	**Total**	**Non-responder**	**Responder**
Number of PDPEs	30	15	45.00	31	22
Years of exposure	38.18	22.07	60.25	39.42	44.99
Annual Rate	0.79	0.68	0.75	0.79	0.49
Relative Risk*					0.65

* The relative risk was calculated based on the annual exacerbation rate observed in mannitol responders compared to the overall Control arm.

The rate ratio presented in the MS does not distinguish between patients receiving mannitol as add-on therapy and those receiving mannitol as second line therapy. Thus, the ERG requested information on the effect of treatment on the exacerbation rate in both subgroups. In their response, the manufacturer presents the results separately for rhDNase users (add-on treatment) and rhDNase non-user unsuitable (second line treatment).

The manufacturer performed a Poisson regression analysis on the rate ratio for PDPE in the overall patient population (corrected for baseline rate and thus not taking into account the differences between historical pulmonary exacerbation rates observed in DMP-CF-302). It showed that rhDNase is not a significant factor for the PDPE rate; there was not sufficient data to run this analysis on the adult population. Due to the low patient numbers in each population there is high uncertainty around the rate ratio in the specific populations. Therefore the analyses have been run on two scenarios: 1) assuming the rate ratio in the 2 subpopulations was the same as for the overall adult population (0.65) and 2) taking the rate ratio as calculated in each subpopulation, 0.91 and 0.47 (see table 24).

Table 24. Rate rationfor pulmonary exacerbation

Patient population		Control			Mannitol			
		N	# PDPE	PDPE rate	N	# PDPE	PDPE rate	RR
All adult	Non-responder	88	30	0.79	107	31	0.79	
	Responder	46	15	0.68	100	22	0.49	0.65
rhDNase user	Non-responder	57	18	0.75	69	20	0.80	
	Responder	28	10	0.75	53	16	0.68	0.91
rhDNase non-user	Non-responder	31	12	0.85	38	11	0.77	
	Responder	18	5	0.57	47	6	0.28	0.37
rhDNase non-user unsuitable	Non-responder	12	4	0.76	16	3	0.42	
	Responder	8	3	0.76	29	5	0.36	0.47

Patient response

The manufacturer indicates in the MS that it is not realistic to assume that the patients will continue treatment with mannitol for the rest of their life irrespective if there is a benefit or not and that it is unlikely that clinicians would prescribe treatment to those patients that get no benefit. Therefore a continuation rule was implemented in the mannitol arm in the cost-effectiveness analysis. Patients on mannitol who are responders will continue treatment for the rest of their life whereas the non-responders will discontinue the treatment with Mannitol and be switched to best supportive care, i.e. the control arm. A response to treatment is defined as a relative increase of at least 5% or an absolute increase of at least 100ml in the FEV1 at week 6 from baseline. The table below (Table 58 in the MS) provides the transition probability of remaining on Mannitol treatment after 6 weeks.

Table 25 Probability of being a responder to Mannitol from DMP-CF-301 and DMP-CF-302 (Adults only)

	Mannitol			Control		
	N	n	%	N	n	%
Responder	207	100	48%	134	46	34%

Again, at the request of the ERG, the manufacturer provided the response percentages separately for rhDNase users (add-on treatment) and rhDNase non-user unsuitable (second line treatment).

Table 26. Responder percentages per subgroup

	All adults		rhDNase user		rhDNase non-user		rhDNase non-user unsuitable	
	n	%	n	%	n	%	n	%
Mannitol	100	48	53	43	47	55	29	64
Control	46	34	28	33	18	37	8	40

Improvement respiratory symptoms

The transition probabilities for improved respiratory symptoms are calculated from the pooled -CF-301 and DMP-CF-302 data. At baseline all patients start in the CF health state and are assumed to remain there till the end of cycle 2 (corresponding to the 14-week visit). The probability of moving to the "improved respiratory symptoms" at this point was based on the number of patient with ≥4 points improvement in their CFQ-R respiratory domain score. The probability of remaining in the "improved respiratory symptoms" health at each next cycle of 12 weeks was based on the number of patients who maintained a ≥4 points improvement in the CFQ-R respiratory domain score at the 26-week visit compared to baseline. Similarly the probability of moving to the "improved respiratory symptoms" at each next cycle was based on the percentage of patients who had <4 points improvement in the CFQ-R respiratory domain score at the 14-week visit and a≥4 points improvement in the CFQ -R respiratory domain score at the 26-week compared to baseline (see table 57 in MS). Patients with missing CFQ-R data were excluded from the analysis.

Table 27 Transition probabilities improvement in respiratory symptoms

Treatment	Respiratory Symptoms	Percentage of patients	n	N
Mannitol	Improved after 3 months	39%	67	170
	Remain improved after 6 months	69%	46	67
	Improved after 6 months but not at 3 months	17%	17	103
Control	Improved after 3 months	46%	55	120
	Remain improved after 6 months	75%	41	55
	Improved after 6 months but not at 3 months	15%	10	65

Again, at the request of the ERG, the manufacturer provided the probabilities to improve separately for rhDNase users (add-on treatment) and rhDNase non-user unsuitable (second line treatment).

Table 28. Transition probabilities improvement in respiratory symptoms – rhDNase users

Treatment	Respiratory Symptoms	% of patients	n	N
Mannitol	Improved after 3 months	33%	34	102
	Remain improved after 6 months	68%	23	34
	Improved after 6 months but not at 3 months	13%	9	68
Control	Improved after 3 months	41%	31	76
	Remain improved after 6 months	74%	23	31
	Improved after 6 months but not at 3 months	20%	9	45

Table 29. Transition probabilities improvement in respiratory symptoms – rhDNase non-users unsuitable

Treatment	Respiratory Symptoms	% of patients	n	N
Mannitol	Improved after 3 months	40%	16	40
	Remain improved after 6 months	63%	10	16
	Improved after 6 months but not at 3 months	25%	6	24
Control	Improved after 3 months	50%	9	18
	Remain improved after 6 months	78%	7	9
	Improved after 6 months but not at 3 months	11%	1	9

COMMENT

Firstly the ERG would like to point out that the effectiveness outcomes used in the clinical effectiveness section of the MS have little relevance for the economic model and/or were not used in the model. In section 5.6 of the MS, the endpoints that would be relevant to the economic model were analysed: FEV1 % predicted, FEV1 responder and per patient per year rate of PDPE. Of these analyses, only the one of responders was actually used in the model. For FEV1 % predicted a regression model was used in the model to allow individual FEV1 % predicted values for 26 weeks, as compared to only changes from baseline in section 5.6. Also, for PDPE the rate ratio of mannitol responders versus control was required for the model but this was not analysed in section 5.6 of the MS.

One of the main assunptions of the model concerns the extrapolation from 26 weeks to life time effects. It was assumed that the initial gain in FEV1 % predicted would be maintained over lifetime (though the

FEV1 % predicted does decrease according to the natural decline). While this is a strong asasumption, some evidence for it is found in the open label phase of study 301. On page 95 of the MS, it is stated that "the adult mannitol population had an increased improvement in FEV_1% predicted over the additional 26 weeks of treatment (4.3% at week 52 vs. 2.9% at week 26) and the patients originally randomised to the control group also showed a 1.1% improvement from week 26 (0.8% at week 52 vs. -0.3% at week 26)."

Additionally, it was assumed that the probabilities of improving respiratory symptoms in the next cycle and of moving from improved to not improved would stay the same over lifetime. This assumption can unfortunately not be tested using the open label data from study 301.

Regarding the natural decline in FEV1 % predicted, in the model a regression equation is used to update a patient's FEV1 % predicted in each cycle. Besides age, the covariate 'hospitalisation in the same quarter' was found to be statistically significant. However, when in a certain quarter a patient is hospitalised, this may occur both before and after the maximum FEV1 % predicted measured in that quarter. While the regression model finds a correlation between the two, this does not mean that causality may be inferred. Also,by translating the covariate 'hospitalisation in the same quarter' into 'exacerbation in the previous cycle' in the model, this causality is in fact implied. Additionally, it should be remarked here that hospitalisation is used as a proxy for severe exacerbation. While often a severe exacerbation may be the reason for a hospitalisation in CF patients, other reasons are also possible. Thus, the use of hospitalisation as a proxy of severe exacerbation might lead to an overestimation of the number of exacerbations.

For the estimation of the probability of severe exacerbation in the CF population again hospitalisation was used as a proxy for exacerbations. Besides the problem of thus overestimating the probability of a severe exacerbation the ERG is uncertain about the way the exacerbation rate is calculated. Table xxx (and Table 68 from the MS) presents the number of observed quarters with either no or at least 1 hospital day (3979 and 1344 respectively) and the number of patients with either 0 or at least 1 hospital day (1190 and 729 respectively, total 1919). Usually a yearly hospitalisation rate would be calculated as the number of hospitalisations divided by the total observed time in years. However, here it is calculated as the total observed time (in quarters) that contains at least 1 hospitalisation, divided by the total number of patients at risk of a hospitalisation. The ERG questions the validity of this estimate, and would have used the same table to arrive at a different hospitalisation rate.. If we consider the 1344 quarters with a hospitalisation as the number of event (assuming that no more than one hospitalisation occurs per quarter), and divide this by the total number of observed quarters (3979+1344=5323) we arrive at a event rate of 0.252 per patient-quarter which is 1.01 per patient-year.

Patients that have an exacerbation who also have a Bcc infection have an increased chance of dying. However, patients experiencing an exacerbation who have no Bcc infection do not have an increased mortality compared to patients without an exacerbation. The ERG questions this assumption. This implicit assumption in the model may be explained by the fact that when a patient experiences an exacerbation, first it is determined whether or not the patient dies (based on the pre-exacerbation FEV1 % predicted) and only in the living patients is the FEV1 % predicted decreased due to the exacerbation. However, it is not feasible for the ERG to change this in the model. After it is assessed that a patient does not die, first it is assessed whether they improve and then whether they are a responder. Based on these two events the FEV1 % predicted is estimated. Thus, it would be necessary to restructure the model completely in order to first estimate the decline in FEV1 % predicted due to the exacerbation and then assess whether the patient dies, based on this decreased FEV1 % predicted. We expect however that the impact will relatively small, since the increased probability of dying would merely be moved forward 1 time cycle.

For the calculation of the effect of treatment on the rate of exacerbations, the PDPE (Protocol Defined Pulmonary Exacerbation) rates have been used. This implies that the rate ratio of PDPE in mannitol versus control may be used as a proxy for the rate ratio of having a severe exacerbation. It is difficult to assess whether such proxy will be an over- or underestimation. In the 302 study report, we find the following results (note that no distinction is made between responders and non-responders):

- A 15% reduction in the annualized rate of PDPE was observed in mannitol compared with control when adjusted for pre-specified covariates (rate ratio=0.85, 95% CI 0.51, 1.41,p=0.520). (page 93 of Clinical Study Report DPM-CF-302)
- There was a 25% reduction in the hospitalization (for exacerbation) rates in the mannitol group compared with the control group when adjusted for covariates (Rate ratio=0.75(95% CI 0.42, 1.33), p=0.328). (page 97 of Clinical Study Report DPM-CF-302)

Here we see that the rate ratio for hospitalisation is more favourable for mannitol than the rate ratio based on all PDPEs. In the 301 study report only a rate ratio for the PDPEs is presented: rate ratio 0.74 [95% CI 0.47, 1.18]. (page 142 of Clinical Study Report DPM-CF-301). This rate ratio is more favourable for mannitol than the one found in the 302 study. Unfortunately, no rate ratio is available from the 301 study for the hospitalisation rate.

From the above evidence from the study reports, we conclude that the assumption that the PDPE rate ratio can be used as proxy for the severe exacerbation relative risk is not unreasonable.

The ERG noticed that the PDPE rates presented in table 24 (which is a copy of table 4 of the manufacturer's response to the clarification letter) do not correspond to the rates presented in table 2 of the manufacturer's response.. Below we present the relevant parts of the two tables for easy comparison.

Table 30. Rate ration for pulmonary exacerbation (replication from table 24)

Patient population		Control			Mannitol			
		N	# PDPE	PDPE rate	N	# PDPE	PDPE rate	RR
rhDNase user	Non-responder	57	18	0.75	69	20	0.80	
	Responder	28	10	0.75	53	16	0.68	0.91
rhDNase non-user unsuitable	Non-responder	12	4	0.76	16	3	0.42	
	Responder	8	3	0.76	29	5	0.36	0.47

Table 31. PDPE rate per year in adults according to their rhDNase status

	1.1.1.1.1.1 Pooled population			
	Control		Mannitol	
rhDNAse status	*1.1.1.*	Mean±SD (range)	N	Mean±SD (range)
User	85	0.91±2.10 (0– 11.06)	122	1.09±2.60 (0 – 16.58)
Unsuitable*	20	0.72±1.01 (0 – 2.15)	45	0.36±0.91 (0 – 4.34)

In table 30 that was used to derive the rate ratio of mannitol versus control as input for the model, the PDPE rates in the mannitol group for rhDNases users are 0.80 and 0.68 for non-responders and responders respectively. However, when not split according to response, the rate given in table 31 is 1.09. Given that in both tables the rates are based on the same patients (N=69+53=122), this seems mathematically impossible. A similar problem occurs in the rhDNase users in the control group. Here the rates separated according to response (table 30) are both 0.75, whereas the overall rate (table 31) is 0.91. In the patient group of rhDNase unsuitable non-users, the same inconsistencies emerge. Unfortunately, we cannot check from the clinical study reports which numbers are correct, as they do not contain the PDPE rates per treatment group stratified by rhDNase status (only rate ratios are presented in the clinical study reports).

Regarding the probability of death after an exacerbation in patients with a Bcc infection, the ERG found a small error in the calculation. In the electronic model, the probability to die of CF is multiplied by the rate ratio for exacerbations and Bcc infection. However, this could potentially lead to probabilities larger than 1. The correct approach is to transform the probability into a rate, multiply the rate by the relative risk, and then retransform the rate into a probability. This leads to a smaller probability of death compared to the

one in the model; however, if the initial probability is small, the 2 approaches lead to very similar results. The ERG has corrected this error in the model.

5.2.7 Health related quality of life

In the manufacturer's submission, health related quality of life was assessed via the Revised Cystic Fibrosis Questionnaire (CFQ-R) and Health Utility Index (HUI) in the pivotal clinical trials of mannitol used as basis for the economic model. In order to facilitate cost-effectiveness analysis, a HUI2 global utility score was determined for each patient (only data available from the DMP-CF-302 trial) according to the HUI Procedures Manual. Since the population of interest for the cost-effectiveness analysis is the adult population, only the self administered questionnaire was analysed.

In the cost-effectiveness analysis the HUI2 global utility scores are determined for the "Cystic fibrosis" health state for mannitol and control.

The values used as inputs for the model are determined as follows:

- The baseline utility is the average overall HUI2 global utility score at screening irrespective of the treatment (see Table 71 in MS);
- Next for each patient the change in utility between Visit 3/Week 14 (or the value reported at the termination visit if the HUI2 global utility value is missing at Visit 3/Week 14) and baseline was calculated. The same was done for the change between Visit 4/Week 26 and baseline;
- The average change in utility from baseline was calculated;
- Finally, the HUI2 global utility scores used into the cost-effectiveness analysis is obtained by summing up the average change and the baseline utility for each health state.

The values used in the cost-effectiveness analysis are presented in the table below (see table 74 in MS).

Table 32 Summary of quality-of-life values for cost-effectiveness analysis

Description	Base case value
Distribution baseline utility	0.899
Change in utility from baseline for patients treated with Mannitol with improvement in respiratory symptoms	0.019
Change in utility from baseline for patients treated with supportive care (Control) with improvement in respiratory symptoms	0.009
Change in utility from baseline for patients treated with Mannitol without improvement in respiratory symptoms	-0.022

Description	Base case value
Change in utility from baseline for patients treated with supportive care (Control) without improvement in respiratory symptoms	-0.046
Duration of utility decrement for exacerbation (days)	14
Utility decrement for exacerbation	-0.23
Utility for patients with FEV<30	0.31
Utility for lung transplant patients	0.80

Patients eligible for lung transplant were assumed to have a utility equal to that measured in patients on the lung transplant waiting list. Patients who received a lung transplant were assumed to have an average utility as measured in post bilateral lung transplantation patients from the UK (the average of 0-6; 7-18; 19-36 and >36 months), as reported by Anyanwu et al.[46]

Data from an observational study[45] reported the impact of mild and severe pulmonary exacerbations on health related quality of life measured by EQ5D in a UK population aged 16 years and older. These data were used to value the exacerbation in the model. The duration of the decrement in utility due to exacerbation was assumed to be 14 days (min-max 1-365 days, triangular distribution), based on a UK CF registry in which IV antibiotics use in hospital was recorded.[49]

In the clarification phase the ERG raised the issue that utilities used in the model for comparable health states (RS improved, RS no improvement) are treatment dependent, which seems inconsistent with the finding that treatment was not a significant covariate in predicting HUI based utility scores. In the response to the clarification the manufacturer states that it was decided to keep both cost and utility parameters treatment dependent as all other input parameters were treatment independent. The manufacturer acknowledged that this is a major assumption; hence sensitivity analyses were performed with equal cost and utility.

The table below presents the treatment independent model inputs.

Table 33. Utility input parameters assuming treatment independent utilities (taken from the response to the clarification letter)

Description	Value
Change in utility from baseline for patients with improvement in respiratory symptoms	0.015
Change in utility from baseline for patients l without improvement in respiratory symptoms	-0.031

COMMENT

The ERG considers the use of treatment dependent utility values because of treatment independent values for other input parameters to be an invalid motivation. Thus the ERG states that using treatment independent cost and utility values for the health states should have been used as a base case analysis.

The disutility value due to exacerbation used in the model was based on the utility of a severe exacerbation, according to table 73 in the MS (note that the reference to Bradley[45] in the MS leads to a poster that does not contain quality-of-life data). The ERG notes that throughout the model description, it is not clear which type of exacerbations are considered. From the reference to Bradley for the disutility and the use of hospitalization rate as a proxy for exacerbation rate in the control group[44], we conclude that it is the manufacturer's intention to only include severe exacerbations in the model.

This conclusion is further confirmed by the use of number of days on antibiotics use in hospital as a measure for the duration of the utility decrement. However, in the model the median number of days is used a baseline value, and the observed range of 1 to 365 days is used in the PSA. However, the observed range cannot be used to describe the uncertainty around the *mean* duration. Obviously, the uncertainty range around the *mean* duration should be much smaller. Furthermore, the ERG is not sure about the use of the period of in-hospital antibiotics use as the period for which a utility decrement should be applied. It is reasonable to assume that the patient's utility has not fully been restored at discharge (see for example in COPD exacerbations[52]. The ERG notices that in the conference abstract by Bradley[45] that was part of the submission (ref 78 in MS[20]), the mean number of hospital days for exacerbations is presented, 9.2 days (n=150). Additionally, on average, patients receive a further 4.2 days IV treatment post-hospitalisation. It seems reasonable to assume that during the period of out-hospital IV treatment, the utility decrement should still be applied. Thus the total duration of the utility decrement is 13.4, and thus, our change has negligible impact on the model outcomes. However, the ERG has assumed that a reasonable estimate of the standard error is 20% of the mean, which means an increase in input uncertainty in the PSA.

A note should be made about the reference given for the disutility of an exacerbation, Bradley et al[45]. The ERG was able to retrieve a conference abstract of Bradley et al[45]. However, in this abstract no quality of life data could be found.

5.2.8 Resources and costs

Costs of treatment

The costs of mannitol are £16.88 per day, which includes the costs of the inhalation device. No administration costs apply. Treatment with rhDNase is also £16.88 per day, with no administration costs. (See MS, page 171, table 84) The costs of best supportive care are not included as treatment costs but as health-state costs.

Health-state costs

In the 301 and 302 studies, resource use was recorded from medical records, discharge summaries and patient's diaries. Costs included are concomitant mediation, hospital admissions, day cases, outpatient visits and community visits. In table 34 per treatment arm the % of patients requiring a certain type of health care have been listed, together with the annual rate.

Table 34 Hospital admission, day case, hospital outpatient and community visits

Type of hospitalisation	Control		Mannitol	
	% of patients	Annual rate	% of patients	Annual rate
Hospital admission	32.84%	0.91	24.15%	0.90
Day case	7.46%	0.22	6.76%	0.17
Outpatient	44.03%	3.27	41.55%	3.93
Unkown	26.87%	0.60	32.85%	0.81
No visit/hospitalisation	8.96%	NA	8.50%	NA
Community visits	44.78%	3.17	41.55%	3.42

*Pooled data; adult population, ITT

Table 35 Duration hospital admission

Statistic	Control	Mannitol
Mean	9.91	9.46
StdDev	6.39	6.22
Min	1.00	1.00
Max	37.00	29.00

*Pooled data; adult population, ITT

Resources were costed at patient level. Prices were taken from National reference costs 2008/2009, BNF 59, and PSSRU 2009. The total mean cost per patient over the 26-week trial period are presented in table 36 (see Table 26 from the manufacturer's response to the clarification letter and MS table 82). Cost for patients experiencing a pulmonary exacerbation were much higher than patients without a pulmonary exacerbation during the trial period.

Table 36. Six-month CF treatment cost (update of Table 82 in submission)

	Cost (£)	Mannitol			Control			Total		
		N	Mean	SD	N	Mean	SD	N	Mean	SD
No PDPE in trial period	Medication	166	2,871	4,390	99	2,617	2,713	265	2,776	3,846
	Community visits	166	48	92	99	53	122	265	50	104
	Hospitalisations	166	1,471	4,323	99	1,994	4,474	265	1,666	4,379
	TOTAL	166	**4,391**	7,136	99	**4,664**	5,492	265	4,493	6,560
PDPE in trial period	Medication	41	4,797	3,919	35	3,976	4,047	76	4,419	3,973
	Community visits	41	62	93	35	53	99	76	58	95
	Hospitalisations	41	7,994	6,829	35	6,325	7,561	76	7,225	7,176
	TOTAL	41	12,852	7,959	35	10,354	10,445	76	11,702	9,210
All patients	Medication	207	3,253	4,360	134	2,972	3,157	341	3,142	3,929
	Community visits	207	51	92	134	53	116	341	52	102
	Hospitalisations	207	2,763	5,551	134	3,125	5,745	341	2,905	5,622
	TOTAL	207	6,067	8,032	134	6,150	7,510	341	6,100	7,820

Pooled data; adult population, ITT

The day to day costs excluding CF medication for CF patients without an exacerbation are approximately £26/day over a 6 month period. For patients with one exacerbation, this cost increases to approximately £58/day. A large proportion of this cost can be attributed to hospitalisations. In the model, patients in the "Cystic Fibrosis" and "CF – Improved respiratory symptoms" accumilate the same, treatment specific, health care costs: £ 4,391 for the mannitol arm and £4,664 for the control arm.

The health care costs presented in the MS do not distinguish between patients receiving mannitol as add-on therapy and those receiving mannitol as second line therapy/in those unsuitable for rhDNAse. Thus, the ERG requested information on the health care costs specific to both subgroups. In their response, the manufacturer presents the results separately for rhDNase users (add-on treatment) and rhDNase non-user unsuitable (second line treatment).

The manufacturer provided instead treatment costs for rhDNase users and rhDNase non-users, both suitable and unsuitable. This was based on a univariate analysis that showed that rhDNase use was a significant factor in overall 6-month treatment costs (excluding primary CF medication), but suitability to rhDNase was not significant (see Response to clarification letter, appendix C for details). Hence the 6-month treatment cost for each arm for patients who did not experience a pulmonary exacerbation were split for rhDNase users and non-users (see Table 37) and it was assumed by the manufacturer that the rhDNase non-user unsuitable population would have the same cost as all rhDNase non-users.

Table 37. Mean 6-month CF-treatment cost (£)

	All adults (N=341)	rhDNase user (N=207)	rhDNase non-user (N=134)
Mannitol	4,391	**5,703**	**2,678**
Control	4,664	**5,389**	**3,279**
Total	4,493	5,574	2,871

Costs of exacerbations

The costs for a pulmonary exacerbation were estimated based on patients with one exacerbation, irrespective of the treatment arm the patient was in (See table 38, MS Table 83). The cost of a pulmonary exacerbation was calculated by taking the mean overall cost for patients experiencing 1 PDPE (£ 10608) and subtracting the mean cost for all patients not having a PDPE during the 26-week time period (£4,493), thus arriving at a cost per exacerbation of £ 6,115 .

Table 38 Costs associated with a patient experiencing 1 pulmonary exacerbation

Cost (£)	**Mannitol (N=30)**		**Control (N=25)**		**Total (N=55)**	
	Mean	SD	Mean	SD	Mean	SD
Medication	4,303	4,088	3,925	4,452	4,131	4,221
Community visits	58	79	64	112	61	95
Hospitalisations	6,564	6,081	6,238	7,906	6,416	6,904
TOTAL	10,925	7,451	10,227	11,509	10,608	9,424

Costs of lung transplant

Lung transplants were included in the model, even though these were not performed during the clinical study. This was due to the short duration of the study, but in real life it is likely that a several CF patients will receive a lung transplant. The cost of a lung transplant were adapted from the National Schedule of Reference Costs using the elective inpatient HRG code DZ01Z corresponding to lung transplant (see MS section 6.5.1).

The follow-up cost after a lung transplant were taken from a UK study which reported the mean cost up to 15 years after lung transplant in 1999 UK pounds sterling at an annual discount rate of 6%.[46] This mean total costs was adjusted to 2009 price level and corrected to the 3.5% inflation rate. Each patient undergoing a lung transplant received the mean follow-up LT costs regardless of the patient's survival after the lung transplant.

Thus, the cost of a lung transplantation were estimated at £ 35,458, and the post lung transplant treatment costs at £ 87,431.

COMMENT

The resource use data was prospectively collected. No counts of resource use were presented, nor a list of unit costs used; only the sources from which the unit costs were taken. More details should have been provided to check the validity over the overall health state costs.

The cost per day of rhDNase according to the most recent BNF (BNF 61) is £16.55 and so the ERG has changed this value in the base case analysis.

The manufacturer used treatment specific costs for the base case analysis, but used the same costs for both treatment groups in a scenario analysis. (see 5.2.10.2) Rather than different costs for mannitol group and control group, the ERG would have expected costs specific to health state. Table 49 in appendix C in the response to the clarification letter shows that patients with improved respiratory symptoms have mean costs of £4374 versus patients without improved symptoms of £4949. The difference between these 2 groups is not statistically significant, but neither is the cost difference between the mannitol group and the control group. Thus, a more natural, and more common way of adding cost to the model would have been to use health state-specific costs. Unfortunately, we have costs either stratified according to respiratory symptoms status *or* according to rhDNase status, both not for both. The ERG has therefore calculated the ratio of the improvement-specific costs to the overall mean costs £4493 (table 37). From this we found that patients with improved RS symptoms have 93% of the overall mean costs and patients with no improved RS symptoms 105% . We have assumed that these percentages also apply to the rhDNase specific overall mean costs.

Furthermore, the ERG was also not convinced by the manufacturer's argument that for the rhDNase unsuitable patients the costs of rhDNase users could be used, as there was no statistically significant difference between suitable and unsuitable patients. Again, according to such logic, the costs should also not have been stratified according to treatment. From table 49 in the response to the clarification letter, we derived that the mean costs for rhDNase unsuitable patients were £4177. See table 39 for the final cost estimates derived by the ERG. Note that the standard deviation reported in the table was derived from the confidence intervals reported in table 49 in the response to the clarification letter, and that the same standard deviation is assumed for both improved and not-improved patients.

Table 39. Mean 6-month CF-treatment cost (£) used by ERG

	rhDNase user (SD)	rhDNase non-user unsuitable (SD)
Total	5574 (6873)	4177 (7737)
RS improved	5175	3,885
RS not improved	5856	4385

5.2.9 Cost effectiveness results

The base-case cost-effectiveness results of the manufacturer's submission are reproduced in the table below.

Table 40 Base case cost-effectiveness results taken from manufacturers submission (pg 182)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Control (baseline)	180,188	11.40	9.75					
Mannitol	211,923	12.10	10.52	31,735	0.70	0.77	41,074	41,074
Control + rhDNase	249,472	11.40	9.75	69,284	0.00	0.00	dominated	dominated
Mannitol+rhDNase	285,858	12.10	10.52	105,670	0.70	0.77	136,768	47,095
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

From these results the manufacturer concluded that mannitol treatment for patients with CF in addition to best supportive care and regardless of rhDNase use in was effective. There was no clear statement regarding the cost-effectiveness. From the table the ERG concluded that the four strategies were considered to be mutually exclusive, since three ICERs were presented.

The ERG mentioned in the clarification letter that in the model an implicit assumption is made that best supportive care is equal to best supportive care + rhDNase in terms of effectiveness. This assumption becomes apparent when looking at the life years and QALYs for both scenarios, which are equal. In their response, the manufacturer states that:

"The submission does not intend to imply that best supportive care is equal to best supportive care plus rhDNase. The assumption made is that the effectiveness of mannitol is independent of the use of rhDNase. This is supported by the fact that rhDNase was not significant in predicting a patient's lung function (see section 9.14).

The ERG is correct that the comparison of Mannitol to Control + rhDNase cannot be made and that the results presented in Table 94 may be misleading. The incremental results reported for the Control + rhDNase should be ignored, as the submission intends to make the following 2 comparisons only (see Table):

1. *Mannitol versus Control*
2. *Mannitol + rhDNase versus Control + rhDNase"*

In the response to the clarification letter the manufacturer submitted the following basecase cost-effectiveness estimates (table 41):

Table 41. Base case result (update of Table 94 of submission)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incr (QALYs)
Control	180,188	11.40	9.75					
Mannitol	211,923	12.10	10.52	31,735	0.70	0.77	41,074	41,074
Control + rhDNase	249,472	11.40	9.75	~~69,284~~	~~0.00~~	~~0.00~~	~~dominated~~	~~dominated~~
Mannitol + rhDNase	285,858	12.10	10.52	36,386	0.70	0.77	~~136,768~~	47,095
ICER, incremental cost-effectiveness ratio; incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years								

Additionally, based on the population defined in the scope, the ERG suggested in the clarification phase that the economic results should be separately reported for the two separate populations/comparisons. Thus, to be consistent with the scope the ERG suggested redoing the analyses and reporting as follows:

- the cost-effectiveness of mannitol+rhDNase vs. rhDNase+BSC for CF patients using rhDNase (i.e. mannitol as add-on therapy);
- the cost-effectiveness of mannitol monotherapy vs. BSC for CF patients who are ineligible, intolerant or inadequately responsive to rhDNase (i.e. mannitol as second-line therapy).

In the response to the clarification letter the manufacturer provided the results of the requested additional analyses (see tables 42 and 43 below)

Table 42. Results rhDNase user

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)
RR exacerbation based on total adult population							
Control + rhDNase	261,529	11.23	9.62				
Mannitol + rhDNase	305,008	11.99	10.42	43,479	0.76	0.80	54,329
RR exacerbation based on rhDNase users adult population							
Control + rhDNase	261,529	11.23	9.62				
Mannitol + rhDNase	310,013	11.84	10.27	48,484	0.62	0.65	74,140
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years							

Table 43. Results rhDNase non-user unsuitable

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)
RR exacerbation based on total adult population							
Control	145,255	11.15	9.53				
Mannitol	184,944	12.50	10.96	39,689	1.35	1.43	27,673
RR exacerbation based on unsuitable adult population							
Control	145,255	11.15	9.53				
Mannitol	177,161	12.68	11.14	31,906	1.53	1.61	19,828
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years							

Subgroup analysis

The manufacturer conducted 2 subgroup analyses, one based on lung function and the other based on mannitol response. In the first subgroup analysis, patients were stratified according to baseline FEV1 % predicted into four groups. The analysis shows that the ICER decreases as the baseline lung function decreases.

Table 44 Results subgroup analysis by lung function

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
ppFEV1 >=80								
Control (baseline)	266,516	17.02	14.71					
Mannitol	309,189	17.78	15.56	42,673	0.76	0.84	50,688	50,688
Control + rhDNase	371,397	17.02	14.71	104,882	0.00	0.00	dominated	dominated
Mannitol+rhDNase	418,734	17.78	15.56	152,219	0.76	0.84	180,808	56,228
ppFEV1 60-79								
Control (baseline)	212,333	13.50	11.67					
Mannitol	249,399	14.27	12.48	37,067	0.77	0.82	45,247	45,247
Control + rhDNase	295,492	13.50	11.67	83,160	0.00	0.00	dominated	dominated
Mannitol+rhDNase	337,312	14.27	12.48	124,979	0.77	0.82	152,562	51,049
ppFEV1 40-59								
Control (baseline)	145,450	9.30	8.00					
Mannitol	173,488	9.97	8.71	28,038	0.67	0.71	39,511	39,511
Control + rhDNase	202,352	9.30	8.00	56,903	0.00	0.00	dominated	dominated
Mannitol+rhDNase	234,732	9.97	8.71	89,283	0.67	0.71	125,818	45,630
ppFEV1 <40								
Control (baseline)	112,260	6.60	5.07					
Mannitol	129,252	7.10	5.79	16,991	0.50	0.72	23,704	23,704
Control + rhDNase	147,083	6.60	5.07	34,823	0.00	0.00	dominated	dominated
Mannitol+rhDNase	169,122	7.10	5.79	56,862	0.50	0.72	79,326	30,746

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

For the subgroup analysis on treatment responders all patients in the mannitol arm were assumed to respond to mannitol treatment, i.e. no patients switched to best supportive care. This analysis shows little impact on the ICERs.

Table 45 Results subgroup analysis Mannitol responders

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Control	180,188	11.40	9.75					
Mannitol	245,351	12.86	11.35	65,163	1.45	1.59	40,857	40,857
Control + rhDNase	249,472	11.40	9.75	69,284	0.00	0.00	dominated	dominated
Mannitol+rhDNase	324,283	12.86	11.35	144,095	1.45	1.59	90,347	46,906

COMMENT

The ERG considers these additional results to be in line with the scope. However, to be consistent, the rate ratios for exacerbations used should be population specific. This implies using rate ratios based on rhDNase users' patient data in the first population and the rate ratios based on unsuitable for rhDNase use patient data for the second population. In conclusion the ERG considers the following ICERs to be relevant:

- the cost-effectiveness of mannitol with rhDNase vs. rhDNase+BSC for CF patients using rhDNase: £ 74,140 per QALY gained.
- the cost-effectiveness of mannitol monotherapy vs. BSC for CF patients who are ineligible, intolerant or inadequately responsive to rhDNase: £ 19,828 per QALY gained

However, the interpretation of these ICERs still is not without any caution. Since treatment independent values for costs and utilities for the health states were only used in a sensitivity analysis on the base case model, the findings above might be biased in favor of the mannitol strategies.

Based on the original submission of the manufacturer, the findings of the ERG, and the response of the manufacturer to the clarification letter, the ERG had to conclude that the baseline and probabilistic sensitivity analyses performed so far were not optimal. For this reason the ERG ran the manufacturers cost-effectiveness model using the following choices:

- The cost-effectiveness of mannitol is analyzed separately for two populations: 1) rhDNase users 2) rhDNase unsuitable patients
- The comparison for the first population is mannitol with rhDNase vs. rhDNase+BSC
- The comparison for the second population is mannitol monotherapy vs. BSC

- Treatment independent and improvement specific values for costs and utilities are used to value health states
- Rate ratios for exacerbations used are population specific.

The results of these ERG analyses are shown in section 5.3.

5.2.10 Sensitivity analyses

The manufacturer assessed the various uncertainties in the economic evaluation through deterministic sensitivity analysis, scenario analysis and probabilistic sensitivity analysis. While the first two show which parameters and assumption have the largest impact on the model outcomes, the latter shows the overall uncertainty around the ICER. Unfortunately, the manufacturer provided all sensitivity analyses and scenario analyses based on the original model, for which the analysis of the trial data were done for all adult patients, instead of separately for the two licensed populations. Consequently, the main relevance of these analyses is not the absolute ICERs they present, but rather the order of magnitude of the impact on the ICERs, since we assume that this relative impact will hold in the ERG base case analyses based on the correct populations. All three type of sensitivity analyses are discussed in the next paragraphs.

5.2.10.1 Deterministic sensitivity analyses

In the manufacturer's submission, an extensive deterministic sensitivity analysis was done to explore the impact of the input parameters on the outcomes one by one. Details on the ranges used in the deterministic can be found in table 86 of the MS (page 173). Many input parameters had little effect on the outcomes, so in the table below A summary of table 95 in the MS) we have included only those analyses where the ICER changed by more than 10%.

Table 46 Main results deterministic sensitivity analysis – Mono-therapy (original analysis submission)

Variable	Min	Max	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Base case	0.00	0.00	31,735	0.77	41,074	31,735	0.77	41,074
Baseline patient characteristics								
FEV1 % predicted CF patient at baseline	90.00	40.00	41,806	0.82	51,133	22,482	0.76	29,600
Estimated FEV1 at week 26								
Regression parameter estimate for yes/no mannitol treatment used to predict the FEV1 % predicted after 26 weeks of treatment	-0.09	3.14	25,506	0.42	60,703	36,148	1.01	35,775
Exacerabation								
Relative risk exacerbation with Mannitol treatment - treatment responders	1.08	0.39	42,971	0.50	85,886	24,062	0.96	25,169
Relative risk of experiencing an exacerbation if patient has experienced an exacerbation in the previous year.	1.00	1.82	34,311	0.71	48,109	30,882	0.79	39,091
Lung transplant & mortality								
Hazard rate ppFEV1	0.97	0.94	28,178	0.60	46,676	34,248	0.89	38,655
Utility								
Utility decrement for exacerbation	0.00	-0.33	31,735	0.76	41,734	31,735	1.23	25,727
Utility no improvement in respiratory symptoms Mannitol arm	0.85	0.90	31,735	0.68	46,554	31,735	0.86	36,925
Utility no improvement in respiratory symptoms Control arm	0.90	0.81	31,735	0.63	50,743	31,735	0.93	34,245
Costs								
Cost of an exacerbation	376	9,012	40,063	0.77	51,854	27,529	0.77	35,631

Table 47 Results varying time horizon and CF mortality – Mono-therapy

Variable	Mannitol cost (£)	Mannitol QALYs	Control cost (£)	Control QALYs	Incremental Cost (£)	Incremental QALY	ICER (£)
Time horizon 1 year	19,223	1.00	16,832	0.99	2,391	0.02	149,587
Time horizon 5 years	73,397	3.77	65,612	3.68	7,785	0.09	86,981
Time horizon 10 years	125,408	6.33	111,435	6.11	13,973	0.22	63,539
Time horizon 20 years	181,196	9.03	158,314	8.57	22,883	0.46	49,907
CF mortality increased by 20%	194,616	9.77	165,137	9.12	29,479	0.64	45,806
CF mortality increased by 50%	173,418	8.73	146,664	8.14	26,754	0.59	44,993

5.2.10.2 Scenario analyses

The manufacturer performed scenario analyses to test various assumptions. We present here only those scenario analyses that showed an impact on the outcomes (see page 189-191 and appendix 9.18 of the MS).

Rate ratio of pulmonary exacerbation and discontinuation rule

From the deterministic sensitivity analysis it was clear that the rate ratio of pulmonary exacerbation for patients receiving mannitol has a high impact on the outcomes of the economic evaluation. Additionally, the manufacturer decided to explore the impact of the discontinuation rule used in the model, i.e. that patients receiving mannitol who show no response after 6 weeks switch to control. Four scenarios were investigated:

In the first scenario the effect of the observed differences in historical rates of pulmonary exacerbations in the DPM-CF-302 was investigated. In this scenario the rate ratios for exacerbations with mannitol responders, and also the effect on FEV1 % predicted was based on the DPM-CF-301 study. Non-responders switch to control after the initial 6 weeks. In the second scenario, the impact if all patients continue mannitol treatment regardless whether they responded to treatment or not was explored. In the third scenario the manufacturer looked at the reduction in the pulmonary exacerbations in the overall mannitol group (responder and non-responders) compared to the control group and the last scenario looks at the overall reduction in pulmonary exacerbations in the DPM-CF-301 study. The results are shown in table 48.

Table 48 Results scenario analysis RR exacerbation and discontinuation rule

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
1) RR based on DPM-CF-301 (RR=0.48)								
Control	180,665	11.44	9.79					
Mannitol	207,593	12.23	10.66	26,928	0.79	0.87	31,090	31,090
Control + rhDNase	250,284	11.44	9.79	69,620	0.00	0.00	dominated	dominated
Mannitol + rhDNase	282,389	12.23	10.66	101,725	0.79	0.87	117,447	37,067
2) No discontinuation rule, RR based on all Mannitol responders (RR=0.65)								
Control	180,188	11.40	9.75					
Mannitol	244,223	12.10	10.62	64,034	0.70	0.87	73,473	73,473
Control + rhDNase	249,472	11.40	9.75	69,284	0.00	0.00	dominated	dominated
Mannitol+ rhDNase	318,192	12.10	10.62	138,004	0.70	0.87	158,346	78,850
3) No discontinuation rule, RR based on all Mannitol patients (RR=0.84)								

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Control	180,188	11.40	9.75					
Mannitol	245,417	12.08	10.60	65,228	0.68	0.85	76,579	76,579
Control + rhDNase	249,472	11.40	9.75	69,284	0.00	0.00	dominated	dominated
Mannitol+ rhDNase	319,262	12.08	10.60	139,074	0.68	0.85	163,275	81,935
4) No discontinuation rule, RR based on all Mannitol patients in DPM-CF-301 (RR=0.69)								
Control	180,188	11.40	9.75					
Mannitol	237,229	12.27	10.80	57,040	0.87	1.05	54,479	54,479
Control + rhDNase	249,472	11.40	9.75	69,284	0.00	0.00	dominated	dominated
Mannitol+ rhDNase	312,312	12.27	10.80	132,124	0.87	1.05	126,191	60,018

Pulmonary exacerbation rate

The following analysis was done based on recent publications that indicate that the pulmonary exacerbation rate in the UK is higher than the pulmonary exacerbation rate observed in the BioGrid data.[44, 45] In this analysis the exacerbation rate was set to 1.50. The manufacturer analyzed the model both in- and excluding the increased risk for pulmonary exacerbations in the previous year.

Table 49 Results scenario analysis using higher exacerbation rate (RR 1.5)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Including the RR for previous exacerbations								
Control	214,150	10.74	9.06					
Mannitol	241,276	11.46	9.87	27,127	0.72	0.81	33,489	33,489
Control + rhDNase	278,811	10.74	9.06	64,662	0.00	0.00	dominated	dominated
Mannitol+ rhDNase	310,912	11.46	9.87	96,762	0.72	0.81	119,455	39,629
Excluding the RR for previous exacerbations								
Control	192,375	11.19	9.53					
Mannitol	223,282	11.87	10.28	30,907	0.67	0.75	41,022	41,022
Control + rhDNase	260,184	11.19	9.53	67,809	0.00	0.00	dominated	dominated
Mannitol+ rhDNase	295,660	11.87	10.28	103,285	0.67	0.75	137,086	47,085

CF costs and utilities

The difference between the mannitol and control arm in cost and utility was small. We investigated the impact if mannitol had the same cost for regular CF treatment (other than treatment of pulmonary exacerbations) and same utility.

Table 50 Results scenario analysis identical cost and utilities

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Control	176,333	11.40	9.88					
Mannitol	211,230	12.10	10.54	34,897	0.70	0.66	52,573	52,573
Control + rhDNase	245,617	11.40	9.88	69,284	0.00	0.00	dominated	dominated
Mannitol + rhDNase	285,165	12.10	10.54	108,832	0.70	0.66	163,957	59,580
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

5.2.10.3 Manufacturer's conclusion in original submission

From the above deterministic sensitivity analyses and scenario analyses that were part of the original submission, the manufacturer concluded that the model was most sensitive the rate ratio of a pulmonary exacerbation when responding to mannitol treatment. This was caused by the high uncertainty around this parameter (mean 0.65; 95% CI 0.39-1.08). The scenario analyses also indicated that the discontinuation rule has a significant impact on the ICER. In addition to the effect of pulmonary exacerbations the detrimental effects of this on a patient's quality of life was another important driver.

Also, the manufacturer considers, of all parameters relating to lung function, the effect of mannitol on the change in FEV1 % predicted after 26 weeks and the hazard rate for ppFEV1 on CF mortality most influential.

Furthermore, of the utilities, the utility scores for patients with no improvement in respiratory symptoms had the most impact. Finally the patient's FEV1 % predicted at baseline has a significant impact on the model, the ICER being lowest in patients with lower FEV1 % predicted. Of all cost parameters, only the cost to treat a pulmonary exacerbation had a great impact on the ICER.

Thus, the manufacturer concludes that the key drivers of the model are:

- The cost of mannitol and the rate ratio of pulmonary exacerbations in the mannitol arm. This is because an exacerbation has an impact on both costs and QALY's.

- The impact of pulmonary exacerbations on a patient's QoL
- The patient's FEV1 % predicted when initiating mannitol treatment
- The improvement in FEV1 % predicted caused by mannitol
- The hazard rate of FEV1 % predicted
- Utility for patients without improvement in respiratory symptoms

5.2.10.4 Additional scenario analyses after clarification letter

In the clarification letter, the ERG asked the manufacturer to conduct an additional scenario analysis including withdrawal rate for switching to control treatment. In their response, the manufacturer showed that at week 14 8% of mannitol responders had withdrawn from treatment and during the next 12 weeks an additional 7.6% withdrew. Based on these numbers, a new analysis was run, with ICERs very similar to the base case presented by the manufacturer.

Furthermore, the manufacturer was asked in the clarification letter to provide a scenario analysis on the percentage of compliance / adherence to treatment. In their response the manufacturer presented a sensitivity analysis using the mean compliance rate of 85.67% for mannitol monotherapy and 83.45% for mannitol + rhDNase versus 84.41% for control + rhDNase. Based on the observed effect that mean compliance is similar in responders and non-responders it was assumed that compliance has no effect on efficacy.

Table 51. Results sensitivity analysis reduced compliance

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)
Control	180,188	11.40	9.75				
Mannitol	206,406	12.10	10.52	26,218	0.70	0.77	33,934
Control + rhDNase	238,740	11.40	9.75				
Mannitol + rhDNase	267,626	12.10	10.52	28,886	0.70	0.77	37,387
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years							

5.2.10.5 Probabilistic sensitivity analyses

In the manufacturer's submission, a probabilistic sensitivity analysis (PSA) was performed to study the impact of all input uncertainty simultaneously. To this end, probability distributions were specified for all input parameters. We refer the reader to tables 59, 60, 61, 62, 63, 64, 65, 74 and 85 in the MS for all details on distributions and their parameters used for the PSA.

After the clarification letter from the ERG, the manufacturer provided separate analysis of the population of rhDNase users and the rhDNase unsuitable non-users. As a result of these re-analyses, several parameters values used in the PSA also changed. This concerns the probabilities of response and improvement of respiratory symptoms, the rate ratio of an exacerbation for mannitol responders, the regression model predicting FEV1 % predicted at 26 weeks, and the 6-month costs. For the probabilities, beta distributions were defined with number of patients and number of events as parameters. For the rate ratio of exacerbation in mannitol responders, a log-normal distribution was specified, but it was unclear how the parameters of that distribution were derived. For the regression model to predict FEV1 % predicted at week 26, the covariance matrix for the regression parameters was used to derive the required parameter values for the multivariate normal distribution. Finally, for the 6-month costs per subgroup, not enough information was provided in the response to the clarification letter to check the input parameters (standard deviations were presented for mean costs per subgroup *or* per treatment, but not for the combination).

In the MS, a PSA is presented, but as mentioned before, this analysis was not done for the correct patient populations. Thus, we present here only the PSA results reported in the response to the clarification letter. From these, shown below, it can be concluded that these uncertainty analyses are based on using the overall rate ratio for exacerbation (see section 5.2.9 tables 42 and 43). As previously stated the ERG prefers the use of population specific rate ratios for exacerbation, so these PSA should be interpreted cautiously.

Table 52. Results PSA – rhDNase users

Statistic	Cost intervention (Mannitol + rhDNase)	Cost comparator (Control + rhDNase)	Incr cost	QALY intervention (Mannitol + rhDNase)	QALY comparator (Control + rhDNase)	Incr QALY	ICER
Mean	305,261	261,509	43,752	9.66	8.79	0.87	53,796
Median	284,047	240,292	44,916	9.69	8.83	0.85	51,715
StDev	68,345	74,395	11,530	0.83	0.86	0.30	281,899
Min	218,565	173,330	-41,580	6.85	5.79	-0.23	-7,548,421
Max	757,057	775,782	84,594	12.10	11.94	1.98	4,271,375
2.5% percentile	233,988	185,765	18,399	7.97	7.06	0.26	14,553
97.5% percentile	482,411	465,971	62,567	11.26	10.43	1.48	132,662

Table 53. Results PSA – rhDNase non-users unsuitable to rhDNase

Statistic	Cost intervention (Mannitol)	Cost comparator (Control)	Incr cost	QALY intervention (Mannitol)	QALY comparator (Control)	Incr QALY	ICER
Mean	185,480	145,698	39,782	10.28	8.77	1.51	30,080
Median	166,269	123,889	42,339	10.32	8.74	1.51	27,666
StDev	63,061	70,831	16,888	0.92	0.97	0.47	19,706
Min	104,624	61,315	-55,480	7.01	5.76	0.20	-35,753
Max	535,095	559,419	134,498	13.39	12.22	3.03	226,289
2.5% percentile	120,432	72,244	-3,784	8.46	6.85	0.56	-1,988
97.5% percentile	365,795	338,087	62,627	12.03	10.69	2.44	77,176

As mentioned at the end of section 5.2.9, the ERG defined a new base case, for which also a PSA was performed (see section 5.3).

COMMENT

In general, the ERG agrees with the conclusions of the manufacturer about the key drivers of the cost-effectiveness results. It is clear that all parameters related to exacerbations play an important role. It is for that reason that the ERG is surprised by the rather narrow interval around the baseline exacerbation rate that was used in the deterministic sensitivity analysis. This rate is based on an observational study in Australia. It was assumed that the rate found in that study could be applied to the control groups in this study, both for the BSC group and the rhDNase + BSC group. One might ask whether the results from this Australian study can be transferred to the UK setting. The exacerbation rate will probably depend on the sort of care that constitutes BSC and there might be differences between Australia and the UK in that regard. Furthermore, it concerns an observational study, in which hospitalizations are used as a proxy for exacerbations. However, exacerbations are not the only reason why CF patients might need a hospital admission, and thus the found baseline rate might be an overestimation. The ERG has therefore performed an additional scenario analysis on the baseline exacerbation rate to see how the extent of the impact on the ICER (see section 5.3).

Regarding the results of varying the time horizon and the CF mortality, we see a few striking results in table 47. Regarding the time horizon, we notice that the ICER decreases for longer time horizons. This is a reasonable result. However, it is striking that with a time horizon of 1 year, 1 QALY is accumulated, which seems unreasonable given the baseline utility of a CF patient. When the ERG ran the model with a 1 year time horizon, we found the same result.

For the various values for increased CF mortality, we also notice remarkable results. When assuming a 20% increase, the ICER increases compared to the base line ICER of £41074. However, when the mortality increases further to a 50% increase, now the ICER becomes smaller than the ICER with the 20% mortality increase. The ERG ran the same scenarios to check for possible typing errors in the

table, but we found the same results. The ERG has found no plausible explanation for the phenomenon.

One of the scenario analyses of the manufacturer concerns the baseline exacerbation rate. That rate is in the model set to 0.7, based on the Australian observational study. The manufacturer suggests, based on a UK study by Jarad et al., that this baseline rate might be too low.[53] The UK study mentions an exacerbation rate of 1.5, which was used in the scenario analysis presented by the manufacturer (Table 49) However, the ERG beliefs that the rate quoted from the study by Jarad et al should be carefully interpreted. In that study, 599 exacerbations occurred in the 341 patients included in the analysis. This led to an estimate of the exacerbation rate of 1.5 However, it was also mentioned that 129 patients did not have an exacerbation, meaning that the 599 exacerbations occurred in only 212 patients. Or, in other words, 212 of the 599 exacerbations were 'first' exacerbation (i.e. first within the observation period). Since we are looking for a baseline exacerbation rate, on which a relative risk will be applied for subsequent exacerbations, we are interested in estimating the 'first exacerbation' rate. To this end, we require the number of patient years by which to divide the 212 exacerbations. This latter value is unfortunately not available, as we would need the observed time until the 'first' exacerbation. Other reasons why the rate of 1.5 should be considered cautiously is that the study used IV antibiotics use as a proxy for exacerbation, and IV antibiotics use could be either in the hospital or at home. Jarad et al. mention, however, that in their hospital 98% of IV antibiotics in CF patients is given for exacerbations, which would imply that IV antibiotics is a good proxy for exacerbations.[53]
It is interesting to see in table 49 that only increasing the baseline exacerbation rate of 1.5 leads to a 20% decrease of the ICER, since now more exacerbations may be prevented by the use of mannitol. If however the rate ratio for subsequent exacerbations is set to 1 (in line with the idea that the baseline rate of 1.5 represents an overall event rate), the ICERs are back to (approximately) their original values.

Finally, the ERG found several errors concerning the parameter values for the distributions used in the PSA.

For a few variables (the four utility values describing change from baseline, depending on improvement and treatment) the MS contains different parameter values than in the electronic model. Since the ERG does not have the data to calculate the parameter values, we assume that the values in the electronic model are correct, given the magnitude of the SEs compared to the means.

Furthermore, for the utility decrement due to exacerbation, the ERG did not understand the parameter values for the beta distribution. According to the ERG, the decrement of 0.23 is found by subtracting 0.61 (SE 0.075) from 0.84 (SE 0.025). The SEs can be derived from the confidence intervals presented in table 73 of the MS. Thus, the overall SE of the decrement is 0.0707. Based on this mean and SE, the parameters of the beta distribution were calculated (α=8.08, β=27.05).

For the distribution of the duration of an exacerbation, an important error was made. The range observed in the population [1-361] was used to specify the distribution. However, this range represents first-order uncertainty, whereas a PSA deals with second order uncertainty. Since no data was available to derive a SE, we have assumed that the SE would be 20% of the mean.

A similar error was made in the distributions used for the various cost variables. For all of them, the standard deviations of the population distribution (i.e. first order uncertainty) were used as measure of second order uncertainty (i.e. the standard error of the mean costs). Thus, we had to derive standard errors (SE) by dividing the SDs by the square root of N (see tbale 54). For all variables, gamma distributions were defined based on the presented mean and SEs. These have been used in the ERG base case analysis (see section 5.3).

Table 54 Standard errors for cost variables

Variable	Mean	SD	N	SE
Cost lung TX	35458	35458 (based on assumption MS of exponential distribution)	56	4738
Cost post lung TX	87431	143376 (study showed all SDs approx 1.65*mean)[46]	677	5514
Cost exacerbation	6115	SD 1 exacerbation 9424, =55, SE 1271 SD no exacerbation 6560, N=265, SE 403		1333
6-month cost rhDnase users improved RS	5175	6874	74*	799
6-month cost rhDnase users not improved RS	5856	6874	85*	746
6-month cost rhDnase unsuitable improved RS	3885	7737	30**	1413
6-month cost rhDnase unsuitable not improved RS	4386	7737	25**	1547

* N rhDNase users total 159. From improvement RS data, 46.4% shows improvement. **N rhDNase unsuitable total 55. From improvement RS data, 55.2% shows improvement.

5.2.11 Model validation

The manufacturer states in the submission that internal validation and debugging of the model was performed using the following validation procedures::

- The model concept and structural assumptions were reviewed by CF specialty physicians and modeling experts from universities in the UK
- Clinical data, utilities and resource use data were double extracted and double checked by at two statisticians/health economists.
- Calculations in the model were checked by two statisticians/health economists.
- Extreme tests were performed to check the plausibility of model outcomes. Extreme testing was applied to the following parameters: treatment efficacy, cost of CF medication, mortality, exacerbation rate, transplant rates, transition probabilities (improvement in respiratory symptoms), discount rates, and utilities.

Furthermore, the reported outcomes of the pooled DMP-301-CF and DMP-302-CF adult population and the result of the microsimulation (100,000 trials) after 26 weeks comparing mannitol mono-therapy with best supportive care, were compared by the manufacturer (Table 87 of MS).

Table 55 Summary of model results compared with clinical data

Outcome	Clinical trial result		Model result	
	Control	Bronchitol	Control	Bronchitol
Lung function ($ppFEV_1$ at baseline)	58.38	59.82	59.27	59.27
Change in $ppFEV_1$	-0.02*	2.55*	-0.86	1.59
% of patients with ≥1 exacerbations after 26 weeks	26%	20%	32%	27%
Exacerbation rate	0.75	0.63	0.76	0.64
Responder	34%	48%	34%	48%
Survival	100%	100%	100%	100%
% of patients with lung transplant	0%	0%	0%	0%
QALYs	0.45	0.45	0.43	0.44

*calculated using mixed model repeated measures analysis of DPM-CF-301 and DPM-CF-302 using imputed height.

Overall the observed clinical trial results correspond well to the modeled result. The difference between the modeled change in FEV1 % predicted after 26 weeks of treatment and the observed clinical result relates to the fact that the model predicts the FEV1 % predicted based on a patient's characteristics rather than implementing the observed change in the clinical trial. Finally, as expected the improvement in FEV1 % predicted in the mannitol arm is lower than in the clinical trial, because in model patients are switched to best supportive care (Control) after 6 weeks in case if they do not respond to mannitol treatment. Note that the difference between the groups is approximately the same for the trial results and the model results.

The model calculations show a slightly higher percentage of patients with at least one exacerbation than observed in the clinical trial, while the exacerbation rate is approximately the same as in the trial. As expected the modeled exacerbation rate for mannitol is slightly higher than observed in the clinical trial because of cross-over to the control arm in case the patient does not respond to mannitol. The observed difference in QALY relates to the incorporation of the utility decrement for pulmonary exacerbations in model.

Since the only difference in the model between the mono-therapy and the add-on therapy to rhDNase relates to the cost of rhDNase the modeled clinical outcomes for the add-on arms are identical to those for the respective mono-therapy arms.

COMMENT

From the manufacturer's description it is not clear how many experts have reviewed the model, and how extensive their review was. Also, no insight is given into the findings of these experts.

Even though the calculations in the model have been checked by two persons, the ERG found various smaller. Thus, the ERG must conclude that the validation was limited and not thorough enough, leaving question marks with respect to the mathematical validity of the model.

It is however reassuring to see that, despite the errors found, at least for a time horizon of 26 weeks the model produces outcomes similar to those found in the clinical studies

5.3 Additional work undertaken by the ERG

Provide details of any additional work conducted by the ERG in relation to cost effectiveness. If the results of any of the additional work affect the size of the ICER, refer the reader to the summary table in Section 6.

New base case analysis

Based on several remarks made in section 5.2 of this report, the ERG defined a new base case analysis:

- The cost-effectiveness of mannitol is analysed separately for two populations: 1) rhDNase users 2) rhDNase unsuitable patients
  - The comparison for the first population is mannitol with rhDNase vs. rhDNase+BSC
  - The comparison for the second population is mannitol monotherapy vs. BSC
- Treatment independent and improvement specific values for costs and utilities are used to value health states
- Relative risks for exacerbations used are population specific

- Costs of rhDNase are changed from £16.88 to the most recent price of £16.55 (BNF 61).
- The hazard ration for FEV1 % predicted % predicted is now based on Cox model with only FEV1 % predicted as explanatory variable: HR 0.952
- The probability of dying for patients with Bcc infection and exacerbation was adjusted as the relative risk was applied to the probability instead of mortality rate.
- Parameters of the beta distribution for a utility decrement due to exacerbation were adjusted.
- Duration of utility decrement was slightly adjusted and a new distribution was defined to reflect second order uncertainty.
- Parameters of the gamma distributions of the cost estimates were adjusted to reflect second order uncertainty.

Table 56 shows all input parameters that were changed compared to the original models provided by the manufacturer in the clarification stage

Table 56 Input parameters for ERG base case (only parameters that change compared to the manufacturer's analysis are presented)

Variable	Mean	SE	Distribution	Remarks
Cost lung TX	35458	4738	Gamma	
Cost post lung TX	87431	5514	Gamma	
Cost exacerbation	6115	1333		
6-month cost rhDnase users improved RS	5175	799	Gamma	
6-month cost rhDnase users not improved RS	5856	746	Gamma	
6-month cost rhDnase unsuitable improved RS	3885	1413	Gamma	
6-month cost rhDnase unsuitable not improved RS	4386	1547	Gamma	
Change in utility from baseline for patients with improvement in respiratory symptoms	0.015	0.015	Normal	For treatment specific utility with improvement original model, SE ≈ mean
Change in utility from baseline for patients without improvement in respiratory symptoms	-0.031	0.015	Normal	For treatment specific utility without improvement original model, SE ≈ 0.5*mean
Duration utility decrement	13.4	20%*mean	Normal	Assumption SD=mean, mean based on 150 patients ⇒ SE 9% of mean. SE inflated to add

				uncertainty due to assumptions made
Utility decrement due to exacerbation	0.23	0.0707	Beta	α=8.08 β= 27.05
Relative risk exacerbations mannitol responders rhDNase users	0.91	0.3	Lognormal	m = -0.1554 s = 0.33 SE based on SE whole population 0.17, fewer patients so increased SE
Relative risk exacerbations mannitol responders rhDNase unsuitable	0.47	0.4	Lognormal	m = -1.035 s = 0.758 SE based on SE whole population 0.17, fewer patients so increased SE
Hazard rate CF mortality FEV1 % predicted	0.952		Lognormal	m = -0.04879 s = 0.00671

Results

Table 57 presents the results of the ERG analysis. As a result of the various changes made the ICERs have increased compared to the rhDNase specific results presented earlier in tables 52 and 53 (section 5.2.10.5). The main reason for the increase is the change from treatment specific costs and utilities to improvement specific (i.e. health state specific) costs and utilities.

Table 57 Results ERG base case analysis

Technologies	***Total costs (£)***	***Total LYG***	***Total QALYs***	***Incr costs (£)***	***Incr LYG***	***Incr QALYs***	***ICER (£) versus baseline (QALYs)***
Results rhDNase users							
Control + rhDNase	*265,610*	*11.27*	*9.79*				
Mannitol + rhDNase	*312,572*	*11.92*	*10.38*	*46,962*	*0.65*	*0.59*	*80,098*
Results rhDNase non-user unsuitable							
Control	*163,748*	*11.00*	*9.53*				
Mannitol	*210,683*	*12.65*	*11.10*	*46,935*	*1.65*	*1.57*	*29,883*
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years							

To assess the uncertainty around these estimates, we have performed a PSA. Figure 5 and 6 present the outcomes of the PSA on the CE-plane, while figure 7 presents the acceptability curves. Figures 5 and 6 show a very different distribution of PSA outcomes on the CE plane. This is caused by the larger confidence intervals for various variables in the rhDNase unsuitable group, as this group was much smaller than the rhDNase user group.

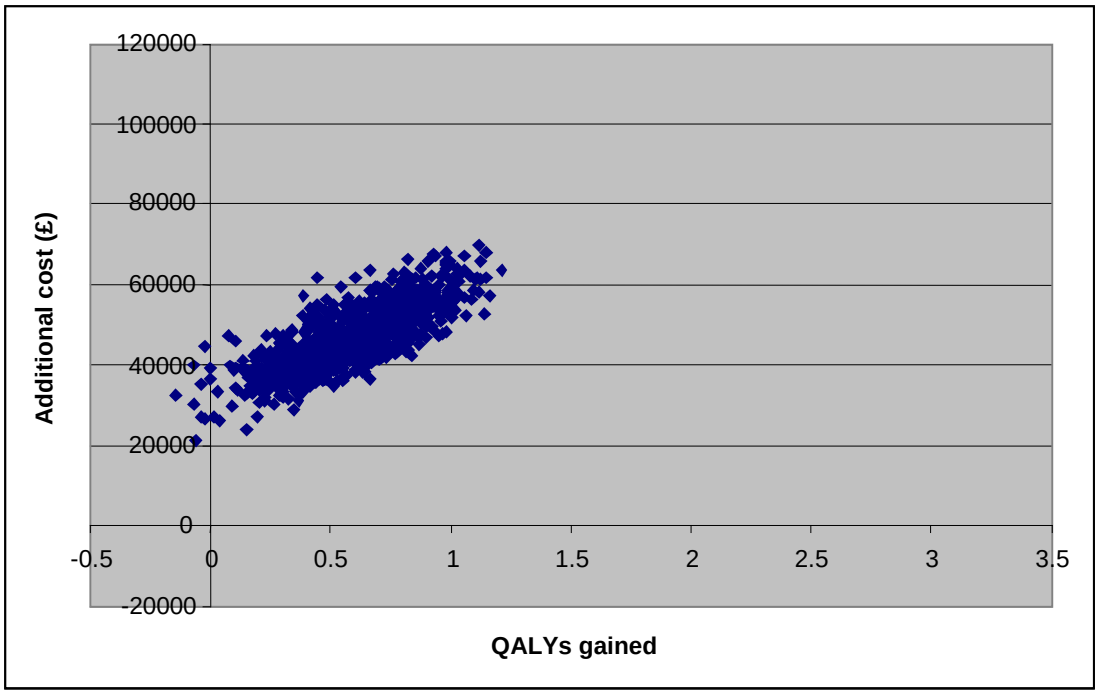

Figure 5 PSA outcomes on CE-plane, rhDNase users

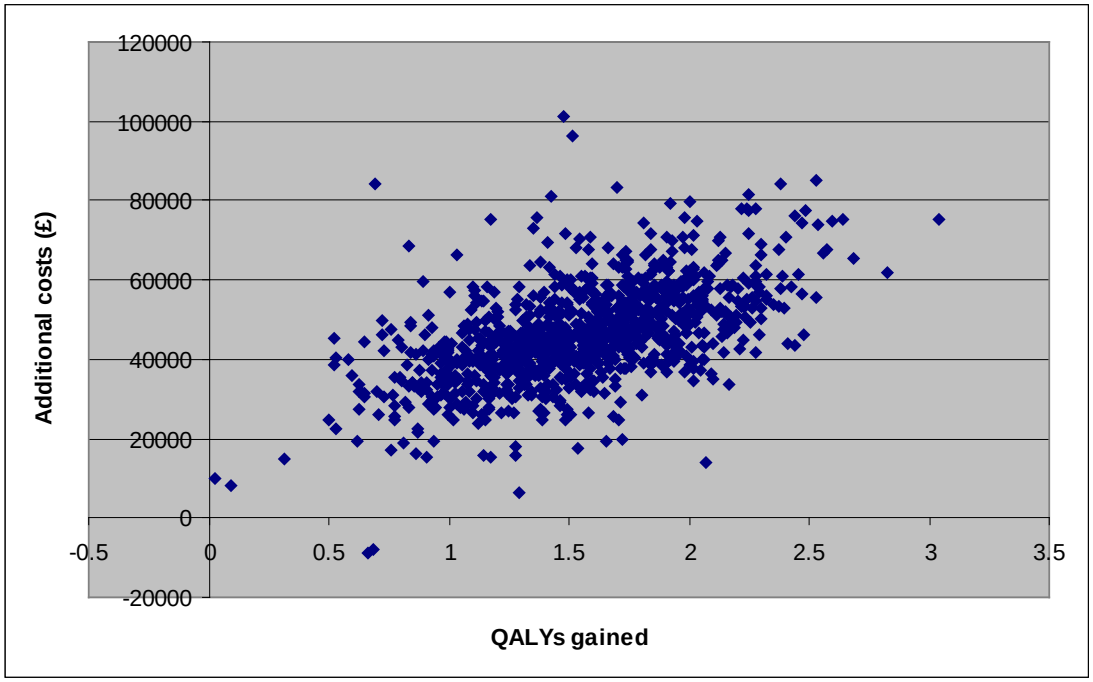

Figure 6 PSA outcomes on CE-plane, rhDNase unsuitable

For the assessment of mannitol in rhDNase users, we find that the probability that the ICER will below a threshold of £30,000 QALYs per year is zero. In rhDNase unsuitable patients, the probability that the ICER is below £20,000 and £30,000 is 5% and 50%, respectively.

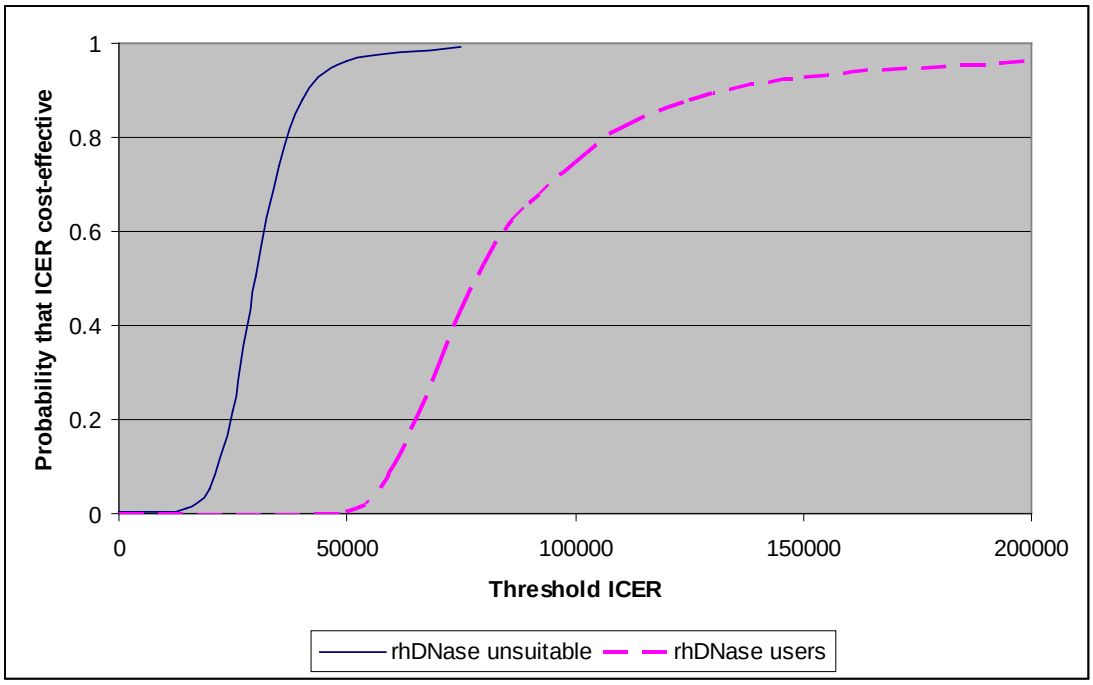

Figure 7 Acceptability curves

Additional scenarios based on ERG base case

The ERG did a few additional analyses. One to vary the exacerbation rate in the control group (rate = 1.5 and 0.5), one to analyse patient subgroups based on FEV1 % predicted at baseline, and one to assess the impact of a shorter time horizon.

The impact of changing the exacerbation rate on the conclusions about the cost-effectiveness of mannitol was small. In rhDNase users, the value of the exacerbation rate has almost no impact, which was to be expected as the rate ratio for mannitol in this group is 0.91. For the rhDNase unsuitable patients, the ICER varied between £22,000 per QALY gained for an exacerbation rate of 1.5 and £37,000 for an exacerbation rate of 0.5.

Subgroup analysis based on FEV1 % predicted at baseline showed only little impact in rhDNase users (the ICER for patients with an FEV1 % predicted <40 was £70,000) and no impact in the rhDNase unsuitable patients.

Finally, we looked at the impact of a shorter time horizon as a proxy for a shorter duration of effectiveness of mannitol (i.e. shorter than life time). It is reasonable to assume that, if mannitol loses effectiveness after a few year, the effects will revert back to the control effects. Also, it reasonable to assume that, with maybe a small lag time, patients will switch from mannitol to control. Thus, from the moment mannitol and control become equal, costs and effects for both arms cancel each other out.

Thus, we can use a sensitivity analysis on time horizon as a proxy for a shorter duration of effectiveness.

For a time horizon of 5 years, the change in ICER is very large. For the rhDNase patients the ICER now becomes £188,551 per QALY gained, and for the rhDNase unsuitable the ICER becomes £90,126 per QALY gained. When the time horizon (and thus duration of mannitol effectiveness) was set to 10 years, the ICERs became £127,625 and £49,854 per QALY gained, respectively.

Evaluation of mannitol versus hypertonic saline

In section 5.2.4 it was mentioned that, because requested in the scope for mannitol, the ERG would attempt to perform a cost-effectiveness analysis of mannitol versus hypertonic saline. After the ERG had performed the indirect comparison it became clear that this was unfortunately not feasible.

The problem lies mainly in the fact that the model used a regression model to predict FEV1 % predicted at 26 weeks, dependent on various covariates, including FEV1 % predicted at baseline. However, the main outcome describing lung function in the indirect comparison was FEV1. After careful consideration, the ERG had to conclude that the effects of hypertonic saline on lung function could not be incorporated into the model. Additionally, the impact on exacerbation could also not be included into the model since the model is based on rate ratios for exacerbations while Elkins et al.[17] reported the mean number of exacerbations per patients.

5.4 Conclusions

Describe the completeness of the MS with regard to relevant cost effectiveness studies and data described in any de novo economic evaluations. Does the submission contain an unbiased estimate of the technology's ICERs in relation to relevant populations, interventions comparators and outcomes? Are there any remaining uncertainties about the reliability of the cost effectiveness evidence? Reference should also be made concerning the extent to which the submitted evidence reflects the decision problem defined in the final scope.

The ERG considers the combination of individual patient data with regression models and microsimulation (model simulates one patient at a time) appropriate to model the heterogeneity in the CF disease process. Using a regression model to estimate FEV1 % predicted also allows for correlations between various clinical parameters e.g. symptoms, response to treatment and age.

However, the ERG considers the estimate of the cost-effectiveness of mannitol provided by the manufacturer not (fully) unbiased for a number of reasons.

Firstly, despite claims that the validity of the model had been checked, this was difficult to verify and there were mistakes, not all of which could be corrected, e.g. QALY in 1st year>1. Although the ERG

did its best to find these errors and correct them where possible in the ERG's own analyses, this still leaves some questions with respect to the integrity of the model as such. However, the ERG believes that remaining imperfections will have limited impact on the major conclusion given the fact that most sensitivity analyses indicate robustness of the findings.

Secondly, costs and utilities were assumed to be treatment specific in the manufacturer's submission. The preferred approach is to define costs and utilities that are health state specific, so that when treatment influences number of patients per health state and the time spent in these states indirectly costs and effects are influenced. Scenario analysis by the manufacturer showed that health state specific costs led to an increase in the ICERs. For that reason, the ERG decided to use the health state specific costs and utilities in the new ERG base case.

Remaining uncertainties about the reliability of the cost effectiveness evidence

Although the exacerbation rate ratio was appropriately obtained from the RCTs, the baseline rate was that of hospitalisation and from an Australian study and the method of estimation was incorrect. However, variation did not affect the ICER much for the rhDNAse users. It could make the ICER change from about £30,000 to £33,000 if the rate decreased from 0.7 to 0.5 in rhDNAse unsuitable patients.

For the calculation of the effect of treatment on the rate of exacerbations, the PDPE (Protocol Defined Pulmonary Exacerbation) rates have been used. This implies that the rate ratio of PDPE in mannitol versus control may be used as a proxy for the rate ratio of having a severe exacerbation. It is difficult to assess whether such proxy will be an over- or underestimation however for the time being the ERG considers this to be best available evidence.

However, the main remaining uncertainty is that of the duration of effectiveness of mannitol treatment. If efficacy is maintained as long as the patient uses mannitol, the ICERs presented by the ERG are valid. If, however, mannitol would lose effectiveness after 5 years, the ICER will increase dramatically, with the ICER for rhDNase unsuitable patients becoming £90,000.

Extent to which the submitted evidence reflects the decision problem defined in the final scope

The submitted evidence did not fully reflect the decision problem defined in the final scope.

The technologies were not appropriately defined to match the scope in terms of rhDNAse use. Data from all adult patients were used to inform both the cost-effectiveness of mannitol versus control and of mannitol plus BSC versus BSC. Also, in the incremental analysis, mannitol plus rhDNAse was

treated as if it could be prescribed to the same population as mannitol alone. Once this was changed through further data being provided by the manufacture, as well as any mistakes were corrected, a new base case was produced by the ERG. This showed that the ICER for mannitol plus rhDNAse in the rhDNAse user population increased (from about £47,000 to about £80,000) and the ICER for mannitol alone in the rhDNAse unsuitable population decreased from about £41,000 to about £30,000.

However, the main limitation of the industry submission is the lack of comparison with hypertonic saline (HS), which was in the scope and the manufacturer admits is current practice at least in some centres. The fact that it might not be used in all centres or even most is insufficient reason to exclude it. Moreover, the other argument put forward that an indirect comparison, which would be needed due to no head-head trials comparing HS with mannitol, was not possible, cannot be tested. This is because the manufacture did not perform a full systematic review of the HS literature. The manufacture also argued that HS and mannitol had different indications, but this is not consistent with the scope and it is also not consistent with the mannitol trials design. If they had different indications then this would imply that HS should have no effect on the disease or symptoms that mannitol has an effect on. However, HS was excluded as a treatment in the trials, which implies that the company believed that it might confound the treatment effect of mannitol. The implications of its exclusion from the trials is therefore reduced confidence that both the effectiveness and cost effectiveness results can be applicable to those also using HS. The implications of it not being a comparator are reduced confidence that mannitol is effective and cost effective in comparison to HS.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Where appropriate, this section should include a table which shows (i) the effect of any major clinical or cost parameter change or structural change on the size of the base-case ICER and (ii) the effect of making all changes simultaneously on the size of the base-case ICER.

The impact of the additional analyses the ERG has undertaken on the ICER is presented in Table 58. In the base case analysis in the MS mannitol is almost equally cost-effective for both comparisons: mannitol vs BSC and mannitol + rhDNase versus BSC + rhDNase. The most influential, and fundamental, change the ERG made, was questioning the use of trial data from the whole adult population for the treatment dependent input parameters for both comparisons. In the clarification phase, the manufacturer provided an analysis with comparison-specific values for the input parameters. This caused the ICERs to differ clearly between the two comparisons.

The definition of an ERG specific base case, with the rate ratio for exacerbation population specific and costs and utilities improvement specific instead of treatment specific, led to an increase in the ICERs for both comparisons.

Finally, the ERG explored the effect of limiting the time horizon as a proxy for a shorter duration of effectiveness of mannitol. This proved to have a very large impact on the ICERs.

Table 58 The effect of any major clinical or cost parameter change or structural change on the size of the base-case ICER

Technologies	**ICER (£))**
Base case manufacturer's submission, analyses based on analysis total adult population	
Mannitol vs Control	41,074
Mannitol + rhDNase vs Control + rhDNase	47,095
Alternative manufacturer, analyses based on subgroup analysis of clinical data	
RR exacerbation based on total adult population	
Mannitol vs Control	*27,673*
Mannitol + rhDNase vs Control + rhDNase	*54,329*
RR exacerbation based on adult subpopulation	
Mannitol vs Control	*19,828*
Mannitol + rhDNase vs Control + rhDNase	*74,140*
Alternative ERG base case ***RR exacerbation population specific*** ***costs and utilities improvement specific instead of treatment specific***	
Mannitol vs Control	*29,883*
Mannitol + rhDNase vs Control + rhDNase	*82,508*

Alternative ERG as above, time horizon 5 years	
Mannitol vs Control	*90,126*
Mannitol + rhDNase vs Control + rhDNase	*188,551*
Alternative ERG as above, time horizon 10 years	
Mannitol vs Control	*49,854*
Mannitol + rhDNase vs Control + rhDNase	*127,625*

7 END OF LIFE

Where appropriate, this section should summarise the manufacturer's case for using the NICE end of life treatment criteria and discuss to what extent the manufacturer's argument is valid.

Not relevant.

8 CONCLUSIONS

The section should focus on any difference(s) of opinion between the manufacturer and the ERG that might influence the size of the ICER. Priority should be focussed on discussing information that will be useful to the Appraisal Committee including strengths, weaknesses and remaining uncertainties. Further summary of evidence is not required in this section.

The industry submission provides evidence from two RCTs comparing mannitol 400mg with mannitol 50mg over 26 weeks in people with CF, aged >= 6 years. Data from these two trials would allow for a comparison of mannitol with best supportive care in both populations (adult rhDNase users and adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase). However, in the MS only lung function is reported for one of the relevant populations for this appraisal: adult rhDNase users. In response to the clarification letter, the ERG received data for both populations, for change in FEV1 (graphs only) and exacerbations. No other data were provided, despite our request for all relevant data for the relevant populations. Results show that in adult rhDNase users, there are no significant differences in exacerbations between mannitol and best supportive care (incidence: RR=1.00 (95% CI: 0.61, 1.66); rate ratio per year: 1.14 (95% CI: 0.75, 1.73)); but mannitol leads to a significant improvement in change in FEV1 (MD=91.77 (95% CI: 30.85, 152.69)) when compared with best supportive care. In adults who are ineligible, intolerant or inadequately responsive to rhDNase, there are no significant differences in exacerbations between mannitol and best supportive care (incidence: RR=0.44 (95% CI: 0.18, 1.10); rate ratio per year: 0.50 (95% CI: 0.18, 1.40)); while mannitol leads to a significant improvement in change in FEV1 (MD=162.32 (95% CI: 51.77, 272.87)) when compared with best supportive care.

In order to compare mannitol with hypertonic saline, the manufacturer performed a feasibility study to determine whether mannitol could be compared with hypertonic saline via indirect comparison. “Based on this feasibility study, an indirect comparison of Bronchitol and hypertonic saline was not felt to be an appropriate analysis in this situation.”

The ERG agrees with most objections of the manufacturer regarding heterogeneity between studies. Nevertheless, given the fact that hypertonic saline was mentioned explicitly in the NICE scope, the ERG would like to present the results of an indirect comparison based on current best available evidence. However, it should also be stressed that some data had to be guessed from graphs, making the analyses even more unreliable. Results of the indirect comparison showed that mannitol is superior to hypertonic saline in terms of change in FEV1 in adult rhDNase users (MD = 23.77 (-64.95, 112.49)), although the difference is not statistically significant. In adults who are ineligible, intolerant, or inadequately responsive to rhDNase, there is no significant difference between mannitol and hypertonic saline in terms of change in FEV1 (MD = 94.32 (-33.67, 222.31)). In terms of exacerbations, hypertonic saline seems superior in adult rhDNase users; although, an indirect comparison is not possible because different outcomes are reported for the different studies.

Regarding the cost-effectiveness analysis the ERG concludes that, in line with good practice in modeling, the manufacturer model generally reflects the natural disease course since it combines individual patient data with regression models and patient level simulation to reflect the heterogeneity in the disease process. It is also, in most ways, in line with the NICE reference case.

However, in terms of rhDNAse use the patient populations defined, the comparisons made, and the data used (especially in the base case analyses) were not according to the scope or good modeling principles. For this reason the ERG conducted its own analyses based on the electronic model as

submitted by the manufacturer and with any mistakes corrected. These analyses showed that for rhDNase users the ICER is £82,508/QALY with a zero probability to be below a threshold of £30,000/QALY. For the rhDNase unsuitable patients the ICER is £29,883/QALY with probabilities of being below the £20,000 and £30,000 of respectively 5% and 50%. Scenario analyses show that relaxing the assumption that mannitol treatment efficacy is lifelong also has a major negative impact on the cost-effectiveness estimate.

8.1 Implications for research

Research recommendations are as follows:

- For adult rhDNase users, data from the available trials should be re-analysed and presented for all outcomes in the NICE scope.
- For adult CF patients for whom rhDNase is unsuitable, a new trial is necessary to provide sufficient evidence for a comparison with BSC.
- For both populations a comparison between mannitol and hypertonic saline should be made, if this is considered a relevant comparator for these populations.
- A cost effectiveness analysis, including hypertonic saline, which, depending on the availability of comparable data for hypertonic saline would make use of alternative data sources and expert opinion. This could also consider the possibility of sequences of treatments.

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Appendix 1: Quality Assessment using ScHARR-TAG economic modelling checklist

Title
Mannitol for treatment of cystic fibrosis

A statement of the problem
Yes, a statement of the problem has been given.

A discussion of the need for modelling
Yes, the need for modelling was determined.

A description of the relevant factors and outcomes
Yes, outcomes and relevant factors of the economic model have been reported and discussed.

A description of model including: type of model; time frame; perspective; and setting
Yes, the submission included a description of the type of model, time frame, perspective and setting.

A description of data sources, with description of respective strengths and weaknesses
Yes, the data sources and respective strengths and weaknesses were reported on described.

Key assumptions relating to model structure and data stated
Yes, key assumptions relating to model structure and data stated were described.

Disease specific factors included within modelling
Yes, disease specific factors were included within the modelling, making the model cystic fibrosis specific.

Validation
Yes, measures undertaken to validate, debug and check the model were reported.

Results
Yes, results were presented.

Sensitivity analysis results
Yes, sensitivity analysis results were presented using deterministic sensitivity analysis, scenario analysis, and probabilistic sensitivity analysis.

Appendix 2: ERG search strategies

Clinical effectiveness

Updated manufacturer clinical effectiveness strategies

Embase (OvidSP): 1980-2011/wk 12
Searched 31/03/11
1 Bronchitol.mp. (20)
2 mannitol.mp. (25571)
3 cystic fibrosis.mp. (41327)
4 1 or 2 (25571)
5 3 and 4 (175) **[hits retrieved before RCT filter]**
6 (randomised or randomized).mp. (461135)
7 5 and 6 (16)

Medline (OvidSP): 1948-2011/03/wk 4
Searched 31/03/11
1 Bronchitol.mp. (0)
2 Mannitol.mp. (16972)
3 cystic fibrosis.mp. (32075)
4 1 or 2 (16972)
5 3 and 4 (76) **[hits retrieved before RCT filter]**
6 (randomised or randomized).mp. (438429)
7 5 and 6 (7)

Cochrane Database of Systematic Reviews (CDSR) (Internet) Issue 3:2011
Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) Issue 1:2011
http://cochranelibrary.com/
Searched 31/03/11

#1	bronchitol	6
#2	mannitol	772
#3	(#1 OR #2)	772
#4	cystic fibrosis	2615
#5	(#3 AND #4)	19

CDSR search retrieved 5 records. (3 reviews)
CENTRAL search retrieved 12 records.

ERG clinical effectiveness strategies

Without RCT filter

Embase (OvidSP): 1980-2011 wk 12
Searched 30/03/11
1 mannitol/ (20500)
2 (mann?t* or manna sugar or Mannazucker or Bronchitol).mp. (25925)
3 69-65-8.rn. (20206)
4 or/1-3 (25925)
5 cystic fibrosis/ (35769)
6 (Cystic fibrosis or mucoviscidosis).mp. (41422)
7 CF.ti,ot. (1919)
8 or/5-7 (42239)

9 4 and 8 (183)

Medline (OvidSP): 1948-2011/03/wk 3
Searched 29/03/11
1 exp Mannitol/ (10275)
2 (mann?t$ or manna sugar or Mannazucker or Bronchitol).ti,ab,ot,hw. (17210)
3 69-65-8.rn. (10227)
4 or/1-3 (17243)
5 cystic fibrosis/ (24869)
6 (Cystic fibrosis or mucoviscidosis).ti,ab,ot,hw. (32128)
7 CF.ti,ot. (1186)
8 or/5-7 (32762)
9 4 and 8 (84)

Cochrane Database of Systematic Reviews (CDSR) (Internet) Issue 3:2011
Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) Issue 1:2011
http://cochranelibrary.com/
Searched 29/03/11
#1 (mannit* or manna sugar or Mannazucker or Bronchitol or Mannistol or 69-65-8) 783
#2 (Cystic fibrosis or mucoviscidosis or CF) 7083
#3 (#1 AND #2) 24

CDSR search retrieved 5 records. (3 reviews)
CENTRAL search retrieved 17 records.

ClinicalTrials.gov (Internet)
http://clinicaltrials.gov/ct2/search/advanced
Searched 29/03/11
Targeted Search option

Conditions	Interventions	Results
(cystic OR fibrosis OR mucoviscidosis OR cf)	(mannitol OR manna sugar OR Mannazucker OR Bronchitol OR Mannistol OR 69-65-8 OR mannit OR mannite)	7
Total		**7**

With an RCT filter

Embase (OvidSP): 1980-2011 wk 12
Searched 30/03/11
1 Random$.tw. or placebo$.mp. or double-blind$.tw. (795083)
2 mannitol/ (20500)
3 (mann?t* or manna sugar or Mannazucker or Bronchitol).mp. (25925)
4 69-65-8.rn. (20206)
5 or/2-4 (25925)
6 cystic fibrosis/ (35769)
7 (Cystic fibrosis or mucoviscidosis).mp. (41422)
8 CF.ti,ot. (1919)
9 or/6-8 (42239)
10 1 and 5 and 9 (41)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7.

Medline (OvidSP): 1948-2011/03/wk 3
Searched 29/03/11

1 randomized controlled trial.pt. (301506)
2 controlled clinical trial.pt. (81952)
3 randomized.ab. (208950)
4 placebo.ab. (122534)
5 randomly.ab. (151788)
6 trial.ab. (215481)
7 groups.ab. (1013143)
8 or/1-7 (1483381)
9 animals/ not (animals/ and humans/) (3469249)
10 8 not 9 (1199381)
11 exp Mannitol/ (10275)
12 (mann?t$ or manna sugar or Mannazucker or Bronchitol).ti,ab,ot,hw. (17210)
13 69-65-8.rn. (10227)
14 or/11-13 (17243)
15 cystic fibrosis/ (24869)
16 (Cystic fibrosis or mucoviscidosis).ti,ab,ot,hw. (32128)
17 CF.ti,ot. (1186)
18 or/15-17 (32762)
19 14 and 18 and 10 (13)

RCT filter adapted from:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org

Indirect and mixed treatment comparisons

Modified manufacturer searches for hypertonic saline + cystic fibrosis

Embase (OvidSP): 2008-2011 wk 15
Searched 18.04.11

1 exp cystic fibrosis/ (35916)
2 (cystic* adj10 fibros*).mp. (42034)
3 mucoviscido*.mp. (2148)
4 exp mucociliary clearance/ (2469)
5 (mucociliar* adj5 clear*).mp. (3348)
6 mucolytic.mp. or exp mucolytic agent/ (47758)
7 (hyperton* adj5 saline).mp. (4757)
8 hypertonic saline.mp. or exp sodium chloride/ (94087)
9 exp hypertonic solution/ (4437)
10 1 or 2 or 3 or 4 or 5 (44915)
11 6 or 7 or 8 or 9 (141732)
12 10 and 11 (1602)
13 Clinical trial/ (831253)
14 Randomized controlled trial/ (293851)
15 Randomization/ (54023)
16 Single blind procedure/ (14180)
17 Double blind procedure/ (102732)
18 Crossover procedure/ (30685)
19 Placebo/ (178791)
20 Randomi?ed controlled trial$.tw. (61444)

21 Rct.tw. (6798)
22 Random allocation.tw. (1030)
23 Randomly allocated.tw. (15459)
24 Allocated randomly.tw. (1703)
25 (allocated adj2 random).tw. (687)
26 Single blind$.tw. (10954)
27 Double blind$.tw. (117777)
28 ((treble or triple) adj blind$).tw. (239)
29 Placebo$.tw. (157993)
30 or/13-29 (1019039)
31 Case study/ (11722)
32 Case report.tw. (199455)
33 Abstract report/ or letter/ (777524)
34 or/31-33 (984918)
35 30 not 34 (988761)
36 35 and 12 (437)
37 limit 36 to yr="2009 -Current" (100)

Medline (OvidSP): 2008-2011/04/wk 1
Searched 18.04.11
1 exp Cystic Fibrosis/ (24974)
2 (cystic* adj10 fibros*).mp. (33452)
3 mucoviscido*.mp. (1747)
4 exp Mucociliary Clearance/ (1824)
5 (mucociliar* adj5 clear*).mp. (2856)
6 mucolytic.mp. or exp Expectorants/ (11859)
7 exp Hypertonic Solutions/ or exp Saline Solution, Hypertonic/ (10169)
8 (hyperton* adj5 saline).mp. (6590)
9 saline solution.mp. or exp Sodium Chloride/ (60013)
10 or/1-5 (35995)
11 or/6-9 (77757)
12 10 and 11 (895)
13 Randomized controlled trials as Topic/ (72191)
14 Randomized controlled trial/ (303438)
15 Random allocation/ (70909)
16 Double blind method/ (109216)
17 Single blind method/ (14791)
18 Clinical trial/ (461126)
19 exp Clinical Trials as Topic/ (239264)
20 or/13-19 (767507)
21 (clinic$ adj trial$1).tw. (152060)
22 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (106561)
23 Placebos/ (29455)
24 Placebo$.tw. (127556)
25 Randomly allocated.tw. (12450)
26 (allocated adj2 random).tw. (657)
27 or/21-26 (320307)
28 20 or 27 (863607)
29 Case report.tw. (156894)
30 Letter/ (710454)
31 Historical article/ (273180)
32 Review of reported cases.pt. (0)
33 Review, multicase.pt. (0)
34 or/29-33 (1130809)
35 28 not 34 (838761)

36 35 and 12 (231)
37 limit 36 to yr="2009 -Current" (21)

Cochrane Database of Systematic Reviews (CDSR) (Internet) Issue 4:2011
Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) Issue 2:2011
http://cochranelibrary.com/
Searched 18/04/11

#1	MeSH descriptor Cystic Fibrosis explode all trees	964	edit	delete				
#2	cystic* NEAR/10 fibros*	2651	edit	delete				
#3	mucoviscido*	64	edit	delete				
#4	MeSH descriptor Mucociliary Clearance explode all trees	166	edit	delete				
#5	mucociliar* NEAR/5 clear*	370	edit	delete				
#6	mucolytic	239	edit	delete				
#7	MeSH descriptor Expectorants explode all trees	848	edit	delete				
#8	MeSH descriptor Hypertonic Solutions explode all trees	489	edit	delete				
#9	MeSH descriptor Saline Solution, Hypertonic explode all trees	315	edit	delete				
#10	hyperton* NEAR/5 saline	647	edit	delete				
#11	saline solution	3221	edit	delete				
#12	MeSH descriptor Sodium Chloride explode all trees	1802	edit	delete				
#13	(#1 OR #2 OR #3 OR #4 OR #5)	2944	edit	delete				
#14	(#6 OR #7 OR #8 OR (#9 AND #10) OR #11 OR #12)	5658	edit	delete				
#15	(#13 AND #14)	184						
#16	(#13 AND #14), from 2009 to 2011	34						

CDSR search retrieved 22 records.
CENTRAL search retrieved 9 records.

Cost effectiveness

Cost effectiveness with mannitol facet

Updated manufacturer strategy
PubMed
Searched 01/04/11
(bronchitol OR mannitol) AND (cystic fibrosis[MeSH Major Topic]) AND (“cost effectiveness”[Title/Abstract] OR cost[Title/Abstract] OR “decision analysis”[Title/Abstract] OR economics[Title/Abstract] OR Markov[Title/Abstract] OR "technology assessment, biomedical"[MeSH Major Topic] OR "cost benefit analysis"[MeSH Major Topic]) AND English[lang] AND ("1990/01/01"[PDAT] : "2010/012/31"[PDAT])
0 hits

ERG strategy
Embase (OvidSP): 1980-2011 wk 12
Searched 31/03/11
1 health-economics/ (30013)
2 exp economic-evaluation/ (165172)
3 exp health-care-cost/ (158727)
4 exp pharmacoeconomics/ (135587)
5 or/1-4 (380311)
6 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (423861)
7 (expenditure$ not energy).ti,ab. (16940)
8 (value adj2 money).ti,ab. (888)
9 budget$.ti,ab. (17951)
10 or/6-9 (442146)
11 5 or 10 (668297)

12 letter.pt. (722795)
13 editorial.pt. (368306)
14 note.pt. (437627)
15 or/12-14 (1528728)
16 11 not 15 (598805)
17 (metabolic adj cost).ti,ab. (640)
18 ((energy or oxygen) adj cost).ti,ab. (2511)
19 ((energy or oxygen) adj expenditure).ti,ab. (14912)
20 or/17-19 (17401)
21 16 not 20 (594863)
22 mannitol/ (20500)
23 (mann?t* or manna sugar or Mannazucker or Bronchitol).mp. (25925)
24 69-65-8.rn. (20206)
25 or/22-24 (25925)
26 cystic fibrosis/ (35769)
27 (Cystic fibrosis or mucoviscidosis).mp. (41422)
28 CF.ti,ot. (1919)
29 or/26-28 (42239)
30 21 and 25 and 29 (14)

Economics filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: EMBASE (Ovid) (weekly search) [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#embase

ERG strategy
Medline (OvidSP): 1948-2011/03/wk 3
Searched 30/03/11
1 economics/ (25967)
2 exp "costs and cost analysis"/ (154502)
3 economics, dental/ (1814)
4 exp "economics, hospital"/ (17024)
5 economics, medical/ (8379)
6 economics, nursing/ (3839)
7 economics, pharmaceutical/ (2195)
8 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (328148)
9 (expenditure$ not energy).ti,ab. (13922)
10 (value adj1 money).ti,ab. (18)
11 budget$.ti,ab. (14178)
12 or/1-11 (439587)
13 ((energy or oxygen) adj cost).ti,ab. (2244)
14 (metabolic adj cost).ti,ab. (578)
15 ((energy or oxygen) adj expenditure).ti,ab. (12814)
16 or/13-15 (15033)
17 12 not 16 (436163)
18 letter.pt. (708104)
19 editorial.pt. (271032)
20 editorial.pt. (271032)
21 historical article.pt. (272043)
22 or/18-20 (979079)
23 17 not 21 (430919)
24 Animals/ (4687500)
25 Humans/ (11591327)
26 23 not (23 and 24) (394952)

27 22 not 25 (100510)
28 exp Mannitol/ (10275)
29 (mann?t$ or manna sugar or Mannazucker or Bronchitol).ti,ab,ot,hw. (17210)
30 69-65-8.rn. (10227)
31 or/28-30 (17243)
32 cystic fibrosis/ (24869)
33 (Cystic fibrosis or mucoviscidosis).ti,ab,ot,hw. (32128)
34 CF.ti,ot. (1186)
35 or/32-34 (32762)
36 31 and 35 (84)
37 36 and 27 (0)

Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED

ERG strategy
Pubmed
Searched 30/03/11
Search using "economics sensitive/broad" filter:
(("mannitol"[MeSH Terms] OR mannit* OR "manna sugar" OR Mannazucker OR Bronchitol OR Mannistol OR 69-65-8) AND ("cystic fibrosis"[MeSH Terms] OR "cystic fibrosis" OR mucoviscidosis OR CF[Title]) AND (costs[tiab] OR cost effective[tiab] OR economic[tiab]))**Hits: 1**

ERG strategy
Pubmed
Searched 30/03/11
Search using "costs sensitive/broad" filter:
(("mannitol"[MeSH Terms] OR mannit* OR "manna sugar" OR Mannazucker OR Bronchitol OR Mannistol OR 69-65-8) AND ("cystic fibrosis"[MeSH Terms] OR "cystic fibrosis" OR mucoviscidosis OR CF[Title]) AND (cost[tiab] OR costs[tiab] OR costs and cost analysis[mh] OR ec[sh]))
Hits: 2

Source of filters:
U.S. National Library of Medicine (NLM). PubMed Health Services Research (HSR) queries using research methodology filters. Bethesda, Maryland: NLM, 2010 [cited 27.04.11] Available from: http://www.nlm.nih.gov/nichsr/hedges/HSR_queries_table.html

Cost effectiveness without mannitol facet

Manufacturer second strategy
PubMed
Searched 31/03/11
(cystic fibrosis[MeSH Major Topic]) AND ("cost effectiveness"[Title/Abstract] OR cost[Title/Abstract] OR "decision analysis"[Title/Abstract] OR economics[Title/Abstract] OR Markov[Title/Abstract] OR "technology assessment, biomedical"[MeSH Major Topic] OR "cost benefit analysis"[MeSH Major Topic]) AND English[lang] AND ("1990/01/01"[PDAT] : "2010/012/31"[PDAT])
198 hits

Manufacturer third strategy
PubMed up to 01.04.11
Searched 31/03/11

(cystic fibrosis[MeSH Major Topic]) AND (“cost effectiveness”[Title/Abstract] OR cost[Title/Abstract] OR “decision analysis”[Title/Abstract] OR economics[Title/Abstract] OR Markov[Title/Abstract] OR "technology assessment, biomedical"[MeSH Major Topic] OR "cost benefit analysis"[MeSH Major Topic]) NOT (screening[Title/Abstract] OR diagnosis[Title/Abstract]) AND English[lang] AND ("1990/01/01"[PDAT] : "2010/012/31"[PDAT])
104 hits

Database of Abstracts of Reviews of Effects (DARE) (Internet)
NHS Economic Evaluation Database (NHS EED) (Internet)
Health technology Assessment Database (HTA) (Internet)
http://www.york.ac.uk/inst/crd/
Searched 01.04.11
(cystic fibrosis) AND (cost effectiveness)
65 Hits
DARE: 14
NHS EED: 47
HTA: 4

ERG strategy
Embase (OvidSP): 1980-2011 wk 12
Searched 31/03/11
1 health-economics/ (30013)
2 exp economic-evaluation/ (165172)
3 exp health-care-cost/ (158727)
4 exp pharmacoeconomics/ (135587)
5 or/1-4 (380311)
6 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (423861)
7 (expenditure$ not energy).ti,ab. (16940)
8 (value adj2 money).ti,ab. (888)
9 budget$.ti,ab. (17951)
10 or/6-9 (442146)
11 5 or 10 (668297)
12 letter.pt. (722795)
13 editorial.pt. (368306)
14 note.pt. (437627)
15 or/12-14 (1528728)
16 11 not 15 (598805)
17 (metabolic adj cost).ti,ab. (640)
18 ((energy or oxygen) adj cost).ti,ab. (2511)
19 ((energy or oxygen) adj expenditure).ti,ab. (14912)
20 or/17-19 (17401)
21 16 not 20 (594863)
22 cystic fibrosis/ (35769)
23 (Cystic fibrosis or mucoviscidosis).mp. (41422)
24 CF.ti,ot. (1919)
25 or/22-24 (42239)
26 25 and 21 (1136)

Economics filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: EMBASE (Ovid) (weekly search) [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#embase

ERG strategy

Medline (OvidSP): 1948-2011/03/wk 3
Searched 30/03/11

1 economics/ (25967)
2 exp "costs and cost analysis"/ (154502)
3 economics, dental/ (1814)
4 exp "economics, hospital"/ (17024)
5 economics, medical/ (8379)
6 economics, nursing/ (3839)
7 economics, pharmaceutical/ (2195)
8 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (328148)
9 (expenditure$ not energy).ti,ab. (13922)
10 (value adj1 money).ti,ab. (18)
11 budget$.ti,ab. (14178)
12 or/1-11 (439587)
13 ((energy or oxygen) adj cost).ti,ab. (2244)
14 (metabolic adj cost).ti,ab. (578)
15 ((energy or oxygen) adj expenditure).ti,ab. (12814)
16 or/13-15 (15033)
17 12 not 16 (436163)
18 letter.pt. (708104)
19 editorial.pt. (271032)
20 editorial.pt. (271032)
21 historical article.pt. (272043)
22 or/18-20 (979079)
23 17 not 21 (430919)
24 Animals/ (4687500)
25 Humans/ (11591327)
26 23 not (23 and 24) (394952)
27 22 not 25 (100510)
28 cystic fibrosis/ (24869)
29 (Cystic fibrosis or mucoviscidosis).ti,ab,ot,hw. (32128)
30 CF.ti,ot. (1186)
31 or/28-30 (32762)
32 31 and 27 (27)

Economic filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED

Pubmed
Searched 30/03/11
Search using “economics sensitive/broad” filter:
(("cystic fibrosis"[MeSH Terms] OR "cystic fibrosis" OR mucoviscidosis OR CF[Title]) AND (costs[tiab] OR cost effective[tiab] OR economic[tiab]))
Hits: 305

Pubmed
Searched 30/03/11
Search using “costs sensitive/broad” filter:
(("cystic fibrosis"[MeSH Terms] OR "cystic fibrosis" OR mucoviscidosis OR CF[Title]) AND (cost[tiab] OR costs[tiab] OR costs and cost analysis[mh] OR ec[sh]))
Hits: 658

U.S. National Library of Medicine (NLM). PubMed Health Services Research (HSR) queries using research methodology filters. Bethesda, Maryland: NLM, 2010 [cited 27.04.11] Available from: http://www.nlm.nih.gov/nichsr/hedges/HSR_queries_table.html

Health Related Quality of Life (HRQL)

Manufacturer HRQL strategies

PubMed
Searched 04/04/11
(cystic fibrosis[MeSH Major Topic]) AND ((quality of life[MeSH Major Topic]) OR ((utility[Title/Abstract]) OR (utilities[Title/Abstract])))
Limited to 1990-to present:
Hits: 192

Database of Abstracts of Reviews of Effects (DARE) (Internet)
NHS Economic Evaluation Database (NHS EED) (Internet)
Health technology Assessment Database (HTA) (Internet)
http://www.york.ac.uk/inst/crd/
Searched 20.04.11

1	(quality of life) OR (utility or utilities)	8175
2	(cystic fibrosis)	250
3	**#1 AND #2**	**80**

ERG HRQL strategies

Pubmed
Searched 04/04/11
#1 (("cystic fibrosis"[MeSH Terms] OR "cystic fibrosis" OR mucoviscidosis OR CF[Title]) AND (hql OR hqol OR “h qol” OR hrqol OR “hr qol” OR “quality of well being” OR sf36 OR “sf 36” OR “short form 36” OR “shortform 36” OR "quality of life"[MeSH Terms] OR “quality of life” OR Utility OR utilities OR CFQ OR “Cystic Fibrosis Questionnaire” OR CFQOL) AND (instrumentation[sh] OR methods[sh] OR Validation Studies[pt] OR Comparative Study[pt] OR “psychometrics”[MeSH] OR psychometr*[tiab] OR clinimetr*[tw] OR clinometr*[tw] OR “outcome assessment (health care)”[MeSH] OR outcome assessment[tiab] OR outcome measure*[tw] OR “observer variation”[MeSH] OR observer variation[tiab] OR “Health Status Indicators”[Mesh] OR “reproducibility of results”[MeSH] OR reproducib*[tiab] OR “discriminant analysis”[MeSH] OR reliab*[tiab] OR unreliab*[tiab] OR valid*[tiab] OR coefficient[tiab] OR homogeneity[tiab] OR homogeneous[tiab] OR “internal consistency”[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR (item[tiab] AND (correlation*[tiab] OR selection*[tiab] OR reduction*[tiab])) OR agreement[tiab] OR precision[tiab] OR imprecision[tiab] OR “precise values”[tiab] OR test–retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intra-observer[tiab] OR intertechnician[tiab] OR inter-technician[tiab] OR intratechnician[tiab] OR intra-technician[tiab] OR interexaminer[tiab] OR inter-examiner[tiab] OR intraexaminer[tiab] OR intra-examiner[tiab] OR interassay[tiab] OR inter-assay[tiab] OR intraassay[tiab] OR intra-assay[tiab] OR interindividual[tiab] OR inter-individual[tiab] OR intraindividual[tiab] OR intra-individual[tiab] OR interparticipant[tiab] OR inter-participant[tiab] OR intraparticipant[tiab] OR intra-participant[tiab] OR kappa[tiab] OR kappa’s[tiab] OR kappas[tiab] OR repeatab*[tiab] OR ((replicab*[tiab] OR repeated[tiab]) AND (measure[tiab] OR measures[tiab] OR findings[tiab] OR result[tiab] OR results[tiab] OR test[tiab] OR tests[tiab])) OR generaliza*[tiab] OR generalisa*[tiab] OR concordance[tiab] OR (intraclass[tiab] AND correlation*[tiab]) OR discriminative[tiab] OR “known group”[tiab] OR factor analysis[tiab] OR factor analyses[tiab] OR dimension*[tiab] OR subscale*[tiab] OR (multitrait[tiab] AND scaling[tiab] AND (analysis[tiab] OR

analyses[tiab])) OR item discriminant[tiab] OR interscale correlation*[tiab] OR error[tiab] OR errors[tiab] OR "individual variability"[tiab] OR (variability[tiab] AND (analysis[tiab] OR values[tiab])) OR (uncertainty[tiab] AND (measurement[tiab] OR measuring[tiab])) OR "standard error of measurement"[tiab] OR sensitiv*[tiab] OR responsive*[tiab] OR ((minimal[tiab] OR minimally[tiab] OR clinical[tiab] OR clinically[tiab]) AND (important[tiab] OR significant[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR (small*[tiab] AND (real[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR meaningful change[tiab] OR "ceiling effect"[tiab] OR "floor effect"[tiab] OR "Item response model"[tiab] OR IRT[tiab] OR Rasch[tiab] OR "Differential item functioning"[tiab] OR DIF[tiab] OR "computer adaptive testing"[tiab] OR "item bank"[tiab] OR "cross-cultural equivalence"[tiab]))
470
#2 ("addresses"[Publication Type] OR "biography"[Publication Type] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])
2780664
#3 #1 NOT #2
457
Date limit from 1990-to present:
443 hits

Instruments filter taken from:
Terwee CB, Jansma EP, Riphagen, II, de Vet HC. Development of a methodological PubMed search filter for finding studies on measurement properties of measurement instruments. Qual Life Res 2009;18(8):1115-23.

Quality of life terms adapted from these two sources:
PROQOLID [Internet]. Lyon, France: MAPI Research Trust, 2011 [cited 04.05.11] Available from: http://www.proqolid.org/
Paisley S, Booth A, Mensinkai S. Chapter 12: Health-related Quality of Life Studies. National Information Center on Health Services Research and Health Care Technology (NICHSR), editor. Etext on Health Technology Assessment (HTA) Information Resources: NICHSR, 2005.

Database of Abstracts of Reviews of Effects (DARE) (Internet)
NHS Economic Evaluation Database (NHS EED) (Internet)
Health technology Assessment Database (HTA) (Internet)
http://www.york.ac.uk/inst/crd/
Searched 20/04/11
1 (cystic OR fibrosis OR mucoviscidosis OR CF) 487
2 (hql OR hqol OR h qol OR hrqol OR hr qol OR quality of well being OR sf36 OR sf 36 OR short form 36 OR shortform 36 OR quality of life OR quality of life OR Utility OR utilities OR CFQ OR Cystic Fibrosis Questionnaire OR CFQOL) 26383
5 #1 AND #2 348

Appendix 3: Philips et al. checklist

Results of assessing the manufacturers report based on the checklist by Phillips et al.

1. Is there a clear statement of the decision problem?

Yes, the decision problem is clearly stated (several options).

2. Is the objective of the evaluation and model specified and consistent with the stated decision problem?

No, treatment with hypertonic saline is missing.

3. Is the primary decision-maker specified?

The term is not used, but implicitly the NHS is assumed

4. Is the perspective of the model stated clearly?

Yes, it is the perspective NHS.

5. Are the model inputs consistent with the stated perspective?

Yes.

6. Has the scope of the model been stated and justified?

No, it is not clearly justified as the scope becomes narrowed down in the clarification letter. The assumption that the patients that are not eligible for rhDNase and rhDNase-non-users do not differ systematically is not justified robustly.

7. Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?

No, it does neither cover hypertonic saline and nor subgroups sufficiently.

8. Is the structure of the model consistent with a coherent theory of the health condition under evaluation?

Yes, in principal; but there is some theory about the health condition for subgroups (e.g. BMI) that is not sufficiently covered.

9. Are the sources of data used to develop the structure of the model specified?

Yes

10. Are the causal relationships described by the model structure justified appropriately?

Yes

11. Are the structural assumptions transparent and justified?

Yes, but the model structure is only validated through the assessment by a single expert.

12. Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?

Yes, although the hypertonic saline treatment option is not included

13. Is there a clear definition of the options under evaluation?

Yes, it is but there is not enough information about what "Best Supportive Care" entails, in particular as the clinical trials are multinational studies.

14. Have all feasible and practical options been evaluated?

No, hypertonic saline is not included

15. Is there justification for the exclusion of feasible options?

Yes, but the justification for exclusion of saline is not robust. A number of articles are mentioned that study hypertonic saline and even with the small numbers of patients, the studies could give important information.

16. Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?

Yes.

17. Is the time horizon of the model sufficient to reflect all important differences between options?

Yes, it's lifelong

18. Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?

Yes, although duration of treatment is assumed to be life-long, but constant efficacy of treatment is not justified.

19. Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?

Yes, they reflect the biological process but disease states are based on improvements and not on the actual health states, which is preferable in Markov models.

20. Is the cycle length defined and justified in terms of the natural history of disease?

Yes

21. Are the data identification methods transparent and appropriate given the objectives of the model?

No. In particular for utility values evidence is unclear. For the key parameter 'utility loss through an exacerbation' only one source is cited. This source is a conference poster abstract (Bradley et al. 2010) that does not mention utility of QoL at all. Furthermore, the RR on exacerbation is based on pooled data and unadjusted for any other covariate.

22. Where choices have been made between data sources, are these justified appropriately?

No, different sources have been chosen (two clinical trials data). But for estimating the treatment effect, a simple linear regression on the pooled data has been conducted.

23. Has particular attention been paid to identifying data for the important parameters in the model?

No, the relative risk on PDPE should have been adjusted for patient characteristics (e.g. age, gender, BMI, disease severity at baseline)

24. Has the quality of the data been assessed appropriately?

Yes.

25. Where expert opinion has been used, are the methods described and justified?

No, it remains unclear how expert opinion has been elicited and incorporated in the study to assess and validate the model structure.

26. Is the data modelling methodology based on justifiable statistical and epidemiological techniques?

No, the RR on exacerbation is the key clinical factor in the analysis. There is a strong indication[1] that this statistic varies by patient characteristics. Sub-group analyses might be desirable.

27. Is the choice of baseline data described and justified?

Yes.

28. Are transition probabilities calculated appropriately?

No, transition probabilities seem to be at least partly unadjusted for personal characteristics

29. Has a half-cycle correction been applied to both cost and outcome?

No.

30. If not, has this omission been justified?

Yes.

[1] Clarification Letter: Appendix B.

31. If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?

No, the model used is very simple. (linear regression on pooled data).

32. Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?

Yes.

33. Have alternative extrapolation assumptions been explored through sensitivity analysis?

Yes.

34. Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?

Yes, but nothing is said about factors influencing continuation, e.g. sex or .age. Furthermore, the benefical effect on lung-function is assumed to be constant over life-time.

35. Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?

Yes, in total four different scenarios with a varying RR and no discontinuation of treatment with Bronchitol.

36. Are the costs incorporated into the model justified?

Yes.

37. Has the source for all costs been described?

Yes

38. Have discount rates been described and justified given the target decision-maker?

Yes

39. Are the utilities incorporated into the model appropriate?

No, the utilities have been defined treatment specific, which is not usual. The preferred approach is health state specific utilities.
A number of commonly (>1/100) reported treatment-related adverse reactions are not includes as they do not lead to a “prolonged diminished QoL” yet for other utilities the model accounts for temporary effects as well. Cough is generally considered beneficial/productive.

40. Is the source for the utility weights referenced?

Yes, it is based mostly on the pivotal clinical trials (HUI2 global utility) data but there is no direct comparison with the reviewed literature. The reference to the source for the utility of exacerbation does not seem correct.

41. Are the methods of derivation for the utility weights justified?

No, the improvement in utility for treated responders might (p179) neither be clinically meaningful (less than .03), nor statistically significant (men of .019 with a SD of .116).

42. Have all data incorporated into the model been described and referenced in sufficient detail?

No, the distributions used for the PSA are not all justified. Some seem to be erroneous (e.g. "RR_Exacerbation_over30" in Table 62) or not enough information is given to replicate (e.g. "u_Exacerbation" in Table 86).

43. Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?

NA.

44. Is the process of data incorporation transparent?

No, not enough information on the pooled clinical trial data and on the utility data.

45. If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?

No, neither described nor justified and at times inconsistent, in a certain parameter is normal in one table and in another table log-normal

46. If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?

While this has not been discussed explicitly, in most instances it is clear that second order uncertainty is reflected. It is also clear that for the cost estimates first order uncertainty has been used to reflect second order uncertainty.

47. Have the four principal types of uncertainty been addressed?

No

Methodological uncertainty is not discussed at all.

Structural uncertainty is not explored: only expert judgment is mentioned to justify the basic structure of the model.

Heterogeneity: insufficient analysis of sub-groups not enough.

Parameter uncertainty has been assessed in the PSA but distributions are not sufficiently discussed.

48. If not, has the omission of particular forms of uncertainty been justified?

No.

49. **Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?**

No. Methodological uncertainty, i.e. gauging the importance or uncertainty of particular analytical steps, has not been assessed sufficiently.

50. Is there evidence that structural uncertainties have been addressed via sensitivity analysis?

Yes, some alternative scenarios has been run for different RR and discontinuation rule in the response to the clarification letter, but it is not clear whether these values have been modelled via a probability distribution.

51. Has heterogeneity been dealt with by running the model separately for different subgroups?

Yes, but only for FEV1% predicted at baseline.

52. Are the methods of assessment of parameter uncertainty appropriate?

Yes.

53. If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?

No. Clearly stated, but not justified.

54. Is there evidence that the mathematical logic of the model has been tested thoroughly before use?

No, this has not been discussed.

55. Are any counterintuitive results from the model explained and justified?

No.

56. If the model has been calibrated against independent data, have any differences been explained and justified?

No, but it has been compared with the pivotal clinical trials data.

57. **Have the results of the model been compared with those of previous models and any differences in results explained?**

No prior models have been discussed.