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A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis

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NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme continues to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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Contents

List of abbreviations i

Executive summary iii

1 Introduction 1
Recombinant human deoxyribonuclease 1
Hypertonic saline 5
Alternative mucolytics 8
The need for the present trial 8
Aims and objectives 9

2 Patients and methods 11
Patients 11
Ethics and consent 11
Methods 11
Economic evaluation 23
Statistical analysis 24

3 Results 27
Airway response to HS 27
Withdrawals from the study 28
Clinical effectiveness 28
Results of the economic evaluation 33
Effectiveness of the washout period 36
Adverse events 39

4 Discussion 41
Interpretation of the results 41
Tolerability of HS 41
Overall evidence for the results 42
Relevance to the NHS 43
Recommendations for future research 43
Conclusion 43

Acknowledgements 45

References 47

Appendix 1 Resource-use checklist for use in interviews 55

Appendix 2 Unit costs used in cost analysis 59

Health Technology Assessment reports published to date 61

Health Technology Assessment Programme 67

List of abbreviations

ASF	airway surface fluid
CEAC	cost-effectiveness acceptability curve
CF	cystic fibrosis
CI	confidence interval
CPT	chest physiotherapy
CT	computed tomography
DGH	district general hospital
DNase	deoxyribonuclease
FCS	15-count breathlessness score
FEV_1	forced expiratory volume in 1 second
$FEF_{25–75}$	forced expiratory flow rate between 25% and 75% of forced vital capacity
FVC	forced vital capacity
HRQoL	health-related quality of life
GEE	generalised estimating equations
GP	general practitioner
HS	hypertonic saline
ICER	incremental cost-effectiveness ratio
IS	isotonic saline
IL-8	interleukin-8
MEF_{25}	mid-expiratory flow rate at 75% of forced vital capacity
MMAD	mass median aerodynamic diameter
NAC	*N*-acetylcysteine
QALY	quality-adjusted life-year
QoL	quality of life
QWB	quality of well-being
R_c	ceiling ratio
rhDNase	recombinant human deoxyribonuclease
RTI	respiratory tract infection
SAB	short-acting bronchodilator
SaO_2	oxygen saturation
SD	standard deviation
VAS	visual analogue scale

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objectives

The objective of this study was to compare the efficacy and cost-effectiveness of daily recombinant human deoxyribonuclease (rhDNase), alternate-day rhDNase and hypertonic saline (HS) in the treatment of children with cystic fibrosis (CF).

Design

This was an open-label, active treatment randomised crossover trial.

Setting and participants

Children with a confirmed diagnosis of CF were recruited from two large CF centres in London, the Great Ormond Street Hospital for Children NHS Trust and the Royal Brompton and Harefield NHS Trust. Two inclusion criteria were age between 5 to 18 years and capacity to perform spirometry. The third inclusion criterion was the requirement to either be currently using rhDNase or to have a forced expiratory volume in 1 second (FEV_1) of less than 70% of the predicted value, which is a generally accepted level for the clinical introduction of rhDNase therapy. Exclusion criteria were inability to attend appointments or take the study medication, known severe hypersensitivity to rhDNase or HS, isolation of *Burkholderia cepacia* in the sputum, receiving research medication as part of another trial within the past 4 weeks and being pregnant or breastfeeding. To ensure that patients were enrolled when they were clinically stable, they had to be free of any lower respiratory tract infection requiring a change in antibiotics, steroids or bronchodilator treatment, during the 14 days before randomisation.

Interventions

Each patient was allocated consecutively to 12 weeks of treatment with once-daily 2.5 mg rhDNase, alternate-day 2.5 mg rhDNase or twice-daily 5 ml of 7% HS, in random order. There was a 2-week washout period between treatments.

Main outcome measures

Patients were assessed at the beginning and end of each of the three treatment periods. The primary outcome measure was FEV_1. Secondary outcome measures were forced vital capacity, number of pulmonary exacerbations, weight gain, quality of life, exercise tolerance, total healthcare cost and relative cost-effectiveness.

Results

A total of 48 children were recruited to the study. Following 12 weeks of treatment, there was a mean increase in FEV_1 over baseline of 16% (standard deviation (SD) 25%), 14% (SD 22%) and 3% (SD 21%) with daily rhDNase, alternate-day rhDNase and HS, respectively. Comparing daily rhDNase with alternate-day rhDNase, there was no evidence of difference between the treatments (2%; 95% confidence interval (CI), –4% to +9%; $p = 0.55$). However, daily rhDNase showed a significantly greater increase in FEV_1 compared with HS (8%; 95% CI, 2% to 14%; $p = 0.01$). The difference in cost between daily rhDNase and alternate-day rhDNase was £513 (95% CI, –£546 to £1510) and between daily rhDNase and HS it was £1409 (95% CI, £440 to £2318). None of the other secondary outcome measures showed significant differences between the treatments.

Conclusions and research recommendations

Alternate-day rhDNase appears to be as effective as daily rhDNase in CF and, on average, reduces health service costs. It appears that 7% HS is not as effective as daily rhDNase, although there was some variation in individual response.

To support our results, a follow-up long-term parallel trial comparing daily rhDNase with alternate-day rhDNase, which includes a health economic analysis, should be performed.

Chapter 1
Introduction

Cystic fibrosis (CF) is the commonest single-gene disorder of Caucasians in the UK. It is estimated that almost 8000 people have the condition, 4500 of those being children.[1] CF is an autosomal recessive disorder. In the UK Caucasian population, 1 in 25 are carriers and about 1 in 2500 have the disease. The prevalence is much lower in non-Caucasians. Most of the morbidity and mortality is from pulmonary disease, which is characterised by bronchial and bronchiolar obstruction by thick tenacious secretions that are difficult to clear.[2] Retention of abnormal airway secretions promotes recurrent respiratory infections, cycles of inflammation and progressive lung damage.[3]

Recombinant human deoxyribonuclease

Background

DNA derived from the disintegration of inflammatory cells, particularly neutrophils, is a major contributor to the viscosity of airway secretions and is present in very high concentrations in the sputum of patients with CF.[4,5] Around 50 years ago, it was shown that bovine pancreatic deoxyribonuclease I (DNase I), an enzyme that cleaves DNA, reduced the viscosity of lung secretions *in vitro*.[6] Based on these observations, bovine pancreatic DNase I (Dornavac or Dornase) was approved in the USA for human use in 1958. Numerous uncontrolled clinical studies in patients with pneumonia and one study in CF suggested that bovine pancreatic DNase I was reasonably safe and effective in reducing the viscosity of lung secretions.[7,8] However, severe adverse respiratory reactions did occasionally happen, perhaps as a consequence of allergic reactions to a foreign protein or of irritation due to contaminating proteases (up to 2% trypsin and chymotrypsin was reported to be present in the final product).[8,9] Consequently this agent lost popularity and its use was stopped without controlled clinical trials ever having been undertaken.

DNase I also occurs naturally in humans. It digests extracellular DNA released during cellular destruction. Using recombinant technology, an exact copy of the native human enzyme was cloned and sequenced in 1990.[10] In the first laboratory studies, recombinant human deoxyribonuclease (rhDNase) hydrolysed extracellular DNA in purulent sputum from CF patients. The viscosity of the sputum, measured qualitatively by the pourability assay, was found to be significantly reduced.[10] Researchers proposed that the reduction in sputum viscoelastic properties observed *in vitro* could benefit patients with CF by improving airway clearance, thus reducing obstruction and the frequency and severity of chest infections. Stable formulations of rhDNase were then developed for aerosol delivery and a series of clinical trials was undertaken to test this hypothesis.

MEDLINE was used to search for all the papers relevant to rhDNase in any clinical context, using 'DNase' as the keyword. All papers relevant to HS were also retrieved combining 'saline' and 'cystic fibrosis'. One of the present authors (Colin Wallis) also undertook a Cochrane review of rhDNase in CF.

Clinical trials of rhDNase

The safety of rhDNase in hospitalised adults with CF had been evaluated in two Phase I dose-escalation studies. No significant adverse events were identified. Neither the enzyme nor antibodies against it were detected in serum.[11,12]

Phase II studies were then performed in the UK and USA, involving patients aged at least 7 years and having mild to moderate CF pulmonary disease.[13,14] In both studies, patients were treated with rhDNase or placebo for 10 days. In the UK study, at day 10, rhDNase treatment (2.5 mg rhDNase twice daily) had significantly increased mean forced expiratory volume in 1 second (FEV_1) by 13% from baseline compared with placebo.[13] Rapid deterioration to baseline occurred within a few days of cessation of therapy.

The Phase II study conducted in the USA produced similar results.[14] CF patients (7 to 51 years of age) were randomly allocated to receive rhDNase 0.6, 2.5 or 10 mg twice a day or placebo. All three dosages of rhDNase resulted in a statistically significant improvement in pulmonary function: mean forced vital capacity (FVC) increased 10–12% and mean FEV_1 increased

12–14%. However, the 2.5-mg and 10-mg rhDNase treatment groups demonstrated the greatest improvement in FEV_1 and FEV_1/FVC ratio. Improvement in quality-of-life (QoL) measures (e.g. dyspnoea score, cough frequency, congestion) was consistently greater among rhDNase-treated patients than among recipients of placebo.

The main objective of the subsequent Phase III study[15] in North America was to test the hypothesis that 2.5 mg of nebulised rhDNase given either once or twice daily would maintain an improvement in lung function and reduce the incidence and severity of lung infections in patients with mild to moderate CF pulmonary disease. The double-blind, randomised placebo-controlled study involved 51 CF centres and 968 CF patients were enrolled. Patients were included if they were 5 years of age or older, had a confirmed diagnosis of CF and had an FVC which was > 40% of the predicted value for height. The patients were then randomly allocated to receive 2.5 mg rhDNase once or twice daily or placebo for 6 months. The initial improvement in FEV_1 during the first month of administration was 7.9% for once-daily, and 9.0% for twice-daily rhDNase administration. At the end of the 6-month period, the improvement in FEV_1 for the placebo group was 0%, for the once-daily group it was 5.8%, and for the twice-daily group it was 5.6%. However, there was a wide variation in individual response. Only 30% of patients treated with rhDNase once daily and 28% of those treated with rhDNase twice daily had an improvement of more than 10% in FEV_1. However, 6% and 7% of patients treated with rhDNase once and twice daily, respectively had a decline of more than 10% in FEV_1.

Administration of 2.5 mg rhDNase, either once or twice daily, reduced the risk of a respiratory infection requiring parenteral antibiotics by 22% and 34%, respectively. However the absolute changes were of little clinical significance. Reductions were obtained in terms of days in hospital, days on parenteral antibiotics, and days at home due to illness for those patients receiving rhDNase. Treated patients also reported improved perception of dyspnoea, overall well-being and CF-related symptoms.

Further studies were undertaken to evaluate the efficacy of rhDNase in patients with severe lung disease (FVC < 40%). This group represents 7% of the CF population, and many are on transplantation waiting lists.[16] In a short-term, placebo-controlled, multicentre study, 70 severely ill patients were randomly allocated to receive either 2.5 mg rhDNase twice daily or placebo for 14 days.[17] After 14 days, there was no statistically significant difference in pulmonary function between the groups. The patient group then continued to receive open-label rhDNase for a further 6 months. At the end of this period clear improvement in pulmonary function was recorded, with a mean increase in percentage predicted FEV_1 and FVC of 9% and 18%, respectively.

Another multicentre, double-blind trial was performed comparing once-daily 2.5 mg rhDNase with placebo in 320 patients with severe lung disease.[18] After 3 months of study, rhDNase was found to produce a statistically significant improvement in pulmonary function. This suggested that the more severely affected patients appear to respond more slowly to therapy. Although there had been concerns that mobilisation of secretions could be hazardous in patients with advanced lung disease, administration of rhDNase did not appear to increase the major complications of CF in these studies. However, when rhDNase was given for 14 days in patients with an acute pulmonary exacerbation there was no improvement in pulmonary function compared with placebo.[19]

The trials showed rhDNase to have an excellent safety profile. Adverse events during rhDNase treatment were generally mild and the drug was well tolerated. The most common adverse events were respiratory. As rhDNase is administered by nebuliser, it is difficult to determine whether these events were causally related to the drug or the method of administration or were part of the disease. In over 1500 patients with CF who have used rhDNase for more than 2 years there have been no reports of anaphylaxis or allergic reactions.[20] Reported side-effects have mostly included pharyngitis and hoarseness.[20] At the lower dose of rhDNase (2.5 mg once or twice daily) there has been no increase in the incidence of haemoptysis. Antibodies have developed in some patients, but the long-term implications of this are unknown. A similar study of 2 years' duration in patients with mild to moderate CF also found no serious, unexpected pulmonary adverse events during treatment with rhDNase.[21]

The clinical trials established the safety and efficacy of aerosolised rhDNase in CF patients over the age of 5 years. Based on available research,[20] rhDNase (Pulmozyme™, Roche Pharmaceuticals, UK) was introduced as a treatment regime in CF at a dose of 2.5 mg once a day At present, most CF centres will consider a trial of rhDNase in children who have a FEV_1 which is < 70% of normal for height.

Some centres place limits on the use of rhDNase in children under 5 years of age due to licensing restrictions and because the safety of this treatment in the developing lung is unknown. Delivery of rhDNase should be via a recommended nebuliser system and compressor.[20] Ultrasonic nebulisers are not recommended for use with rhDNase. Current research indicates that rhDNase should be used on a continuous basis to maintain benefit. It should not be mixed with other drugs, but can be used safely in sequence. Administration should not immediately precede physiotherapy.

Currently rhDNase is widely used in the treatment of CF, but controversies persist. Although many patients improve on treatment, there is marked variation in individual response. Attempts at predicting the outcome for the individual patient on the basis of pretreatment clinical data have failed.[22] Therefore to assess response to rhDNase, most CF centres have developed formal *n*-of-1 trials of treatment to find out who benefits and to justify prescribing the agent.[23] Most centres agree on the outcome measures, namely lung function as measured by spirometry, and the patient's opinion. There is less agreement about the duration of such trials, with periods ranging from 2 weeks to 3 months. Response to rhDNase at 3 months has been shown to be a good predictor of response at 1 year.[24] However, no studies have assessed how response to rhDNase after a shorter duration of time correlates with long-term response.

Long-term effects of rhDNase

The long-term benefit of rhDNase remains controversial.[25] There are only four studies which have assessed this, one randomised[15] and three observational.[21,24,26] The duration of the studies ranges from several months to 2 years. In the best-designed of the studies, Fuchs and colleagues[15] showed that the initial improvement in FEV_1 of approximately 9% declined over the first month and remained stable at between 5% and 6% thereafter. The observational study reported by Shah and colleagues[21] showed a similar change in lung function, which then remained stable over 2 years.

A retrospective review of the effects of rhDNase in children with CF showed that about one-third of children had a sustained improvement in spirometry results of more than 20% over a year, but one-third actually deteriorated.[24] More worryingly, many of the children who got worse actually felt better. There was a good correlation between lung function response at 3 months and 1 year, which suggested sustained benefit.

The most recent long-term study, by Milla,[26] used a different design, in which the change in percentage predicted FEV_1 over time was compared for the periods before and 2 years after the start of rhDNase therapy. There was a more rapid decline of lung function after rhDNase than before. Thus, a beneficial long-term effect of rhDNase has not yet been firmly established.

The effects of rhDNase on lung function not only decrease with time, but also may be completely lost after the medication is terminated. One 6-month treatment study showed that, after rhDNase was stopped, lung function dropped markedly below the initial baseline level.[27] Concern arises as to whether treatment with rhDNase only effects a superficial removal of secretions while, deeper down on the mucosal surface, tissue damage continues as before. This raises the possibility that rhDNase is a 'cosmetic' therapy, which merely masks the process of ongoing destruction in the lungs.[28] It is important to confirm that short-term improvements in lung function caused by rhDNase are not traded off against the potential risk of increased pulmonary inflammation.

Effects of rhDNase on airway inflammation

The initial hope that treating CF patients with rhDNase would lead to a dramatic decrease in the level of airway inflammation has not been realised. When the clinical trials evaluating the efficacy of aerosolised rhDNase in CF were under way, the hypothesis evolved, based on *in vitro* studies, that this form of therapy might actually increase serine protease activity in the airways.[29] Activated neutrophils in the CF lung release large amounts of proteases, particularly elastase and cathepsin G. Free elastase is inactivated, in part, by anti-proteases, such as bronchial secretory leuco-protease inhibitor and α_1-antitrypsin. Another fraction of these cationic enzymes forms inactivated complexes with extracellular DNA.[30] Thus cleavage of DNA may result in a significant release of serine proteases, which may in turn cause enhanced proteolytic activity.[31]

Studies have subsequently examined how treating CF patients with rhDNase affects the neutrophil protease load and interleukin-8 (IL-8) levels in the lung. Rochat and colleagues[32] assessed the effect of 15 days of rhDNase therapy on neutrophil elastase and cathepsin G activity in the sputum. Both showed a rise following start of therapy, although only the rise in cathepsin G activity was significant. Following cessation of therapy, both

showed a moderate decline, in keeping with the findings of Kueppers and Fiel.[29] These findings, however, are contradictory to those reported in other studies.[33,34] Shah and colleagues[33] found a significant increase in elastolytic activity 1 day after the onset of rhDNase therapy. However after 6 months of treatment, neutrophil elastase activity had returned back to normal. Costello and colleagues[34] actually showed a significant decrease in sputum elastase activity at 12 weeks following initiation of rhDNase therapy. This reduction was maintained at 52 weeks. All three studies, however, found that rhDNase did not alter total IL-8 levels in the sputum.

The reason for this conflicting data on protease activity is difficult to explain, but the underlying severity of the disease may be influential. The studies by Shah[33] and Costello[34] and their colleagues included patients with mild to moderate pulmonary disease as indicated by a FVC which was > 40% of predicted. Rochat and colleagues[32] included patients with FEV_1 of 20 to 44% of predicted value, representing moderate to severe lung disease. Several studies have shown a direct relationship between the severity of lung disease and sputum levels of neutrophil elastase.[35,36] CF patients evaluated by Rochat and colleagues[32] had elastase activity levels in sputum samples obtained before initiation of rhDNase therapy that were about one order of magnitude higher than those in the study by Costello.[34] Unfortunately, Rochat and co-workers[32] do not mention lung function data.

Of greater concern are the results of recent *in vitro* work examining the effects of bovine DNase on IL-8 in CF sputum.[37] A previous study suggested that IL-8 does not bind to DNA,[33] although this was not substantiated with data. The previous reports which have shown that rhDNase *in vivo* has no effect on sputum IL-8 concentration have failed to distinguish between IL-8 that is bound to macromolecules and that which is free and therefore biologically active.[32–34]

Extracellular DNA in the airways is known to bind the basic proteases, cathepsin G and neutrophil elastase.[31] Perks and colleagues[37] have shown *in vitro* that the anionic polymer DNA binds to the cationic chemokine IL-8, and prevents it from binding to neutrophil receptors. Bovine DNase *in vitro* increased the proportion of free IL-8 ten-fold and also increased significantly the IL-8-dependent neutrophil chemotactic activity of the sputum supernatants. They suggested that an electrostatic interaction between DNA and IL-8 may limit the inflammatory potential of the latter, but that this interaction was weakened by DNA cleavage by DNase. These findings[37] which had only been presented in abstract form at the commencement of this study have now been published.[38]

Cost-effectiveness of rhDNase

Daily 2.5 mg rhDNase is an expensive therapy, costing about £7442 per patient per year in the UK.[39] Available cost analyses of rhDNase have considered its impact on respiratory tract infection (RTI)-related resource utilisation and costs.[40–42] All the reports were generated by a single international project team[41] which applied local cost data for various countries to reductions in health-care resource utilisation demonstrated in the US study by Fuchs and colleagues.[15] Costs were considered for 24 weeks of rhDNase therapy (2.5 mg once or twice daily) versus placebo in patients with mild to moderate disease. As this was a pre-market trial, the cost of rhDNase was not included in the analyses but was added afterwards in revised calculations.

For the USA,[40] costs of RTI-related resource use were estimated from the bills and discharge summaries of 385 patients with CF. This information was used to construct a cost-prediction model which was then applied to the data of Fuchs and colleagues[15] to estimate inpatient costs. Cost estimates for outpatient antibacterial therapy included drug costs, supplies and associated professional services. Over a 24-week period, the estimated average total cost of care related to RTI was reduced by US$1682 and US$814 with rhDNase once and twice daily, respectively, relative to placebo. Assuming once-daily dosing of rhDNase, the authors speculated that the cost savings would offset approximately one-third the cost of the drug.

A similar range of cost offsets (approximately 17 to 27% of the acquisition cost) was found for rhDNase 2.5 mg once daily in a European cost analysis.[41] The 2.5 mg twice-daily dose was not assessed, as its use is restricted in Europe. Local estimates of unit costs (hospitalisation and antibiotic costs) were determined for patients in France, Germany, Italy and the UK and applied to the RTI-related resource use data of Fuchs and colleagues.[15] Reductions in the costs of RTI-related care (excluding the cost of rhDNase) were estimated to range from about £434 (US$700) in the UK to approximately FF7011 (US$1100) in France. Lower costs of inpatient treatment represented the largest component of these savings.

An informal cost–utility analysis of rhDNase was conducted by a development and evaluation committee of clinicians in the South and West Region of England.[43] Clinical and resource utilisation data from Fuchs and colleagues[15] were used. It was calculated that the net costs (total costs less savings) to the National Health Service (NHS) of prescribing daily rhDNase to CF patients, excluding those with severe disease, would be £5900 per patient per year. The investigators estimated the cost per quality-adjusted life-year (QALY) for rhDNase to be around £25,000. Details of the analysis, however, were not reported.

Another study estimated the cost per life-year gained using daily rhDNase to be approximately £52,500 for all CF patients.[44] However, for those with moderate to severe lung disease (FEV_1 less than 70% of predicted), the cost per life-year gained was estimated at £16,000. The calculations were made on the basis of a model developed from previous studies[15,45–47] to estimate the rate of decline in lung function for CF patients.

The incremental cost-effectiveness of rhDNase relative to standard therapy (i.e. therapy available before the introduction of rhDNase) was studied in Canada.[48] Probabilities and clinical efficacy data were obtained from Fuchs and colleagues,[15] and from data obtained retrospectively from the medical records of 32 patients attending two Canadian CF clinics. Although the addition of rhDNase was consistently more costly than standard therapy, its incremental cost-effectiveness decreased with time. A sub-analysis showed that for the costs of rhDNase to equal those of standard therapy, the daily cost of rhDNase 2.5 mg would need to be reduced from Can$35.00 to Can$15.88.[49]

The studies performed have shown that rhDNase is an important adjunct therapy in the management of CF. It is an effective mucolytic agent that can improve the health and well-being of some patients with CF. An inevitable development of this will be the desire to offer a potentially beneficial therapy to patients with early-stage disease, whether they be infants or older patients with mild disease.[50] However a number of areas still need consideration and study. The long-term effect of rhDNase is not known, and its effects on the growing lung or on the inflammatory process in CF are not clear. It is an expensive agent and the long term cost–benefits are difficult to anticipate. No randomised trials of rhDNase with cost-effectiveness analyses have been undertaken in the UK. As discussed earlier, previous studies in this area have extrapolated using results from the USA trial by Fuchs and colleagues.[15] This can lead to problems due to the differences between the USA and the UK in CF healthcare practice. Also, in the study by Fuchs and colleagues,[15] only RTI-related resource use was assessed. It is often difficult to differentiate RTI-related from non-RTI-related resource use in CF management, for example during inpatient care.

Alternate-day rhDNase

Once-daily 2.5 mg rhDNase, which is the standard dose used in children with CF, has been shown to be as efficacious as twice-daily 2.5 mg rhDNase.[15] There are no studies on the use of alternate-day rhDNase which if equally effective would halve the cost of treatment. Alternate-day rhDNase would also reduce the number of time-consuming nebulisers administered, with the potential to improve adherence and quality of life.

Hypertonic saline

Background

Hypertonic saline (HS) is defined as a solution where the concentration of sodium and chloride ions is greater than that found in 0.9% saline (isotonic saline (IS)). Nebulised HS has been used for decades as an agent to aid airway clearance and sputum induction in a variety of respiratory disorders. Pavia and colleagues[51] showed an increase in mucociliary clearance in patients with chronic bronchitis following the inhalation of 7% HS compared with IS. HS has been shown to improve mucociliary clearance in normal and asthmatic airways.[52] It has also been used in CF as a mucolytic agent to improve airway clearance. However, it is only over the past few years that studies have been done to assess its mode of action and efficacy.

Mechanism of action

HS has a favourable effect on the rheological characteristics of mucus. The effect of 3% HS on the elasticity of mucus in CF has been examined *in vitro*.[53] HS reduced spinnability and sputum rigidity compared with IS. Wills and colleagues[54] have studied the transportability of sputum from patients with CF, using a mucus-depleted bovine tracheal model. They measured the intrinsic transportability of bovine mucus and compared this with the transportability of expectorated sputum. The relative transportability of CF sputum was lower at baseline but increased with the addition of sodium chloride. As this was a closed system, they suggested that there was no change in the hydration of the sputum and the increase in mucus transportability was

due to improvements in both viscosity and elasticity. They concluded that increasing the salt content, rather than the hydration, of sputum may benefit patients with CF by improving mucociliary transport.

The mechanism by which HS enhances mucociliary clearance and sputum expectoration in patients with CF remains unclear. The deposition of HS onto the airway surface is likely to cause a significant change in the osmolarity of the airway surface fluid (ASF) by drawing water into the airway, leading to rehydration of airway secretions.[55] Rehydration of the airway secretions may make the sputum less tenacious, facilitating its expectoration. Even in normal individuals, increased hydration of airway secretions is known to increase mucociliary clearance.[56] In a recent study examining the effect of instillation of 3% HS into the lungs of rabbits, a rapid influx of water from the plasma into the alveolar space was demonstrated.[57] Osmotic equilibrium was complete within 3 minutes. Furthermore, there was no injury to the epithelial or endothelial barriers of the lung. The hyperosmolar challenge also does not appear to be associated with significant increases in vascular permeability. In a study in anaesthetised guinea pigs,[58] tracheal mucus velocity was transiently increased by 122% following the nebulisation of a 14.4% solution of HS. No increase in plasma protein extravasation was detected.

Ziment[59] has postulated that HS breaks the ionic bonds within the mucin gel, thus reducing the effective degree of cross-linking and entanglement and lowering the viscosity and elasticity. With chronic infection, the mucin molecules develop fixed negative charges, resulting in a net repulsion. HS raises the ionic concentration sufficiently to cause a conformational change by increasing shielding of the excess negative charges and limiting repulsion. The result is thought to be a more compact structure of the mucus molecule that leads to more effective clearance.

Clinical studies of HS

Robinson and colleagues[60,61] looked at radiolabelled aerosol clearance to assess changes in mucociliary clearance with nebulised HS in CF patients. Each patient was given radiolabelled aerosol by nebuliser and serial lung scans were performed. Nebulised HS increased radioisotope clearance compared with IS controls. Increasing the concentration of HS had an effect on mucociliary clearance. There was a significant difference between 3% and 12% HS, favouring the higher concentration. There was, however, no significant difference in mucociliary clearance between 7% and 12% HS.

The addition of nebulised amiloride (which blocks the excessive sodium absorption from the ASF) to 7% HS led to no significant additional difference in radioisotope clearance, and amiloride alone was not significantly different from IS. Since HS induces cough in some patients, the effect of cough on mucociliary clearance was also studied to eliminate the possible confounding effect.[60] Each patient was asked to cough voluntarily, such that the number of cough manoeuvres performed was equal to or slightly greater than the maximum number of coughs recorded during the intervention period. The difference in mucociliary clearance between cough alone and HS remained significant. Therefore it was concluded that the improvement in mucociliary clearance by HS was not due to coughing alone.

Riedler and colleagues[62] looked at the effects of HS on sputum expectoration in patients with CF. Ten adolescents with CF, who were receiving inpatient treatment for a pulmonary exacerbation, were enrolled in a controlled crossover clinical trial. Each patient inhaled either IS or 6% HS for 10 minutes, prior to routine physiotherapy. The following day the patients received the alternative solution. Seven patients undertook a second block after 1–5 days. Sputum expectoration from the beginning of the inhalation of HS or IS to the final spirometry measure 60 minutes after chest physiotherapy (CPT) was significantly greater after HS than IS. A clinical score of the patient's own judgement of the efficacy of CPT was also significantly better after HS than IS. However, there was no significant change in spirometry results following either of the two inhalations.

A short-term clinical trial was then undertaken to examine the effects of HS on pulmonary function and symptoms in patients with CF.[63] The patients recruited had moderate to severe lung disease, with FEV_1 between 30 and 70% of predicted value. Individuals were randomly allocated to receive 10 ml of either IS or 6% HS for 2 weeks. Treatments were delivered using a portable nebuliser twice daily, prior to CPT. A total of 52 patients (32 males), with a mean age of 16.2 years (range 7–36 years) completed the study. Following 2 weeks of treatment, there was a significant improvement from baseline in FEV_1 of 15% in patients treated with HS, compared with a change of 2.8% in those on IS therapy. The treatment was well

tolerated. There was a subjective improvement in the effectiveness of CPT reported by those using HS. Furthermore there were also significant improvements in exercise tolerance and quality of sleep. The improvement in lung function with nebulised HS in this study was similar to that reported for rhDNase when inhaled over a 2-week period.[13]

Ballmann and von der Hardt[64] compared nebulised rhDNase with HS in a short-term pilot study. This study has been presented in abstract form, but is yet to be published. A total of 14 CF patients with mild to moderate lung disease (FVC greater than 40%) were enrolled in a crossover study. The two treatments were rhDNase 2.5 mg once daily and 5.85% HS 10 ml twice daily. All patients had 3 weeks of treatment, followed by 3 weeks without treatment (washout), and then repeated the two courses with the other treatment. The treatment order was randomised. The same jet nebuliser system (Pari Master™ with Pari LL™) was used by all patients. There was no carry-over and no phase effect was reported. FEV_1 increased by 7.7% with HS compared with 9.3% with rhDNase. The short-term effects on pulmonary function appeared to be comparable between the two treatments; however the patient numbers were small. The cost for 1 month's treatment with rhDNase was DM2427 compared with DM86 for HS. However, the mean inhalation time was significantly longer with HS (84 minutes a day) compared with rhDNase (11 minutes a day), with the potential problem of poor adherence if this was introduced as part of routine therapy.

In all the studies of HS in CF, the participants have received premedication with an inhaled short-acting bronchodilator (SAB) prior to inhalation of HS, to prevent any significant bronchoconstriction from occurring. HS is a non-specific bronchial irritant that has been used as a provoking agent for tests of bronchial responsiveness in patients with asthma.[65,66] Rodwell and Anderson[67] have reported the effect of a 10% HS challenge in 23 patients with CF who had asthma-like symptoms. For this study, the individuals were selected on the basis of a history of wheeze, breathlessness or cough on exercise or changes in the weather. Up to 30% of the patients showed a fall in FEV_1 of greater than 15% A second group of patients (40%) showed a transient decrease in FEV_1 with a partial spontaneous recovery before the challenge finished. A third group (30%) showed spontaneous recovery during the challenge, with the final FEV_1 recorded at the end of the challenge being significantly higher (4.5%) than immediately prior to the challenge. All groups had a further significant increase in lung function after administration of a SAB at the completion of the challenge.

Adverse events due to HS have been adequately reported in only one study.[63] It was found that both 6% HS and IS caused a similar increase in cough.[63] Intercurrent haemoptysis occurred in three patients on each treatment. One patient in the HS group had to withdraw because of haemoptysis though it was not clear whether this was directly related to treatment. In the HS group one patient complained of chest tightness and one of pharyngitis. This also occurred with the use of 12% HS in another study.[61]

Effects of HS on airway inflammation

The effect of HS on airway inflammation and defences is unclear. If the high-salt hypothesis regarding ASF in CF is correct,[68,69] HS may potentially be harmful. This hypothesis states that in CF patients the ASF has a higher salt concentration than normal, leading to the deactivation in the airways of naturally occurring salt-sensitive peptides such as defensins.[68,69] Defensins are believed to be responsible for the early elimination of bacteria, fungi, and viruses from the airway. Once this primary line of defence has been violated, as has been hypothesised by certain groups with regard to CF,[68,69] a more vigorous and sustained immune response is believed to be evoked, thus causing the migration of large numbers of neutrophils and macrophages into the airway lumen. Any effect of HS on defensins is likely to be more important early in the disease process in delaying the onset of colonisation. Once suppurative lung disease is established, there is likely to be a more significant beneficial effect of HS in removing from the airways the viscous secretions and the pathogens and degradative enzymes contained therein. However, it is also likely that any effect of HS on the ion concentration of the ASF, and hence on salt-sensitive defensin deactivation, is transient and would soon be counteracted by the rapid influx of water into the airway lumen along its osmotic gradient.[57]

From the studies reported so far, HS represents a potential alternative mucolytic therapy for CF. It appears to have a beneficial effect in short-term use and it appears to be safe for the most part. It is certainly cheaper than rhDNase. However, no medium- or long-term studies of HS have been performed in patients with CF. All of the studies involved HS followed by CPT. Robinson and colleagues[61] have shown no difference in

mucociliary clearance between 7% HS and 12% HS. However, 3% HS has been shown to be relatively less effective.[61] Therefore, nebulised 7% HS, twice daily, appears to be an adequate dosage. A Cochrane review of randomised trials has now been set up to determine whether HS improves lung function, exercise tolerance and quality of life, and decreases the incidence of pulmonary exacerbations in patients with CF.[70]

Alternative mucolytics

N-Acetylcysteine

Alternative inhaled mucolytic agents such as *N*-acetylcysteine (NAC) and mannitol have been tried in CF lung disease with varying success. NAC is a widely prescribed mucolytic for patients with CF.[71] It depolymerises mucus *in vitro* by breaking disulphide bridges between macromolecules.[72,73] It is assumed that such a reduction of the tenacity of sputum facilitates its removal from the respiratory tract. However, there are problems with the use of nebulised NAC in CF. First, NAC has been associated with bronchospasm in patients with airway hyper-responsiveness. The routine addition of a bronchodilator to NAC has been advocated.[74] Secondly, NAC has a distinct, unpleasant, sulphurous odour, which may cause problems with adherence to treatment. Despite the fact that NAC is commonly used in CF, published data on its effects are scarce. The randomised controlled trials on nebulised NAC have failed to show a statistically significant or clinically relevant beneficial effect.[75,76] At present, therefore, there is no evidence that nebulised NAC improves lung function or prevents its decline in CF.

Mannitol

Recently, inhaled mannitol has been considered as a mucolytic agent in for use in CF. It is a non-ionic osmotic agent and thought to work in a similar way to HS. It acts by inducing an influx of water into the airway lumen and hence improves hydration of airway secretions,[57,77,78] which in turn is known to increase mucociliary clearance.[56] An early study using inhaled mannitol found an improvement in mucociliary clearance in normal individuals and people with asthma.[79] A follow-up study to investigate its use in non-CF bronchiectatic patients also found a significant increase in mucociliary clearance.[80]

A pilot study was performed to compare the effects of inhaled mannitol and HS in 12 patients with CF.[81] The dose of mannitol used was 300 mg and it was inhaled using a low-resistance device (Dinkihaler; Rhône Poulenc Rorer, USA). The HS dosage was 7 ml of 6% nebulised saline. Two controls were employed: the mannitol control was inhalation from empty capsules through the Dinkihaler, and the HS control was 7 ml of 0.9% nebulised saline. As both mannitol and HS are known to induce coughing in some patients, both control days consisted of placebo inhalation with matched cough. The coughs were matched in terms of number and timing. The patients received each treatment in random order on different days and bronchial mucus clearance was measured using a radioaerosol/gamma camera technique.

The study found that there were significant improvements in bronchial mucus clearance for both mannitol (8.7%) and HS (10%) compared with their controls (2.8% and 3.5%, respectively). The improvements seen with mannitol were of a similar magnitude to those seen with HS. Despite the fact that patients had received premedication with a bronchodilator, small decreases in mean FEV_1 were seen with mannitol and HS. Both of these decreased values were significantly different from their respective control values but not from each other.

Inhaled mannitol has the potential to become a mucolytic therapy in CF. It can be delivered as a dry powder and therefore delivery times could be shorter than for other nebulised mucolytics. However, only one study has been performed in which mannitol was used by CF patients.[81] No short-term trials have assessed lung function changes, or the efficacy or safety of mannitol. Further studies to find the optimal dose of mannitol to be used in CF patients are required before clinical trials are undertaken.

The need for the present trial

Although once-daily rhDNase has been shown to have considerable benefit in trials and clinical use, there is a need to consider other mucolytic therapies. Daily rhDNase is an expensive agent and there is a marked individual variation in response, with only a proportion of patients showing a sustained benefit.[15,24] At present, alternate-day rhDNase and HS appear to be potential alternatives. If alternate-day rhDNase is as effective as daily rhDNase, it would halve the treatment cost and also reduce the number of nebulised treatments the patient needs to take. HS would also be a cheaper alternative to daily rhDNase, but would have disadvantages including increased nebulisation time.

When considering any new therapeutic intervention, a benefit over the current therapy, that is, daily rhDNase, has to be demonstrated to the patient. For individuals with CF, this benefit ideally would be increased survival time. However, as the estimated median predicted lifespan of individuals with CF approaches 40 years,[82] survival time becomes an impractical measure of clinical efficacy. Surrogate markers of increased survival, such as lung function, weight gain, pulmonary exacerbations, and QoL, need to be compared for the proposed interventions.[83] Any adverse and undesirable effects must be excluded. In view of the differences in treatment costs, there is also a need for an economic comparison.

Aims and objectives

The main aim of the study was to test the hypothesis that HS and alternate-day rhDNase are as effective as daily rhDNase in improving respiratory function in children with CF. An additional aim was to estimate the relative costs and cost-effectiveness of daily rhDNase, alternate-day rhDNase and HS, over a 12-week period, for children with CF.

Chapter 2

Patients and methods

Patients

Children with CF, confirmed either by a sweat chloride level of greater than 60 µmol/l or positive genotyping for two known CF disease-producing mutations,[84] were recruited from two large CF centres in London, the Royal Brompton and Harefield NHS Trust and Great Ormond Street Hospital for Children NHS Trust. Inclusion criteria were age between 5 and 18 years, the ability to undergo spirometry, and the requirement to be currently on rhDNase or to have an FEV_1 capacity less than 70% of the predicted value.[85] An FEV_1 of less than 70% of predicted value was arbitrarily chosen as an inclusion criterion because it suggests at least moderate lung disease, and most CF centres would consider a trial of rhDNase when children with CF develop this degree of lung damage. At the time the study was being designed, there was no evidence that rhDNase would benefit patients with early-stage lung disease.

Exclusion criteria were inability to attend appointments or take the study medication, known severe hypersensitivity to rhDNase or HS, and isolation of *Burkholderia cepacia* in the sputum. Certain strains of *B. cepacia* are easily transmissible and have the propensity to cause severe systemic disease and multiple antibiotic resistance.[86,87] Special and rigorous isolation procedures are necessary for CF patients with *B. cepacia* and these patients are seen in separate clinics. For these reasons, isolation of *B. cepacia* in the sputum was deemed an exclusion criterion. Other exclusion criteria included receiving research medication as part of another trial within the previous 4 weeks and being pregnant or breastfeeding. To ensure that patients were enrolled when they were clinically stable, they had to have been free of any lower RTI requiring a change in antibiotics, steroids or bronchodilator treatment during the 14 days before randomisation. This definition of clinical stability has been used in previous rhDNase trials.[14,15]

Ethics and consent

The study was approved by the ethics committees of both hospitals.

A list of eligible patients was obtained from the CF database at each centre. The patients and their parents were telephoned and informed about the trial, and further information was sent to them by post. We approached the parents and patient at their next clinic appointment and discussed with them the purpose of the research, the potential benefits and harms of each treatment, how often the child would need to be seen and how the lead researcher could be contacted. It was emphasised that they could refuse to take part, or could withdraw from the study at any time without prejudice to the child's treatment. Information sheets, approved by the ethics committees of the study centres, were given. After the families had returned home they were able to consider entering the study and to telephone the lead researcher with any questions regarding it. We arranged to meet with the parents and patient at their subsequent clinic appointment to discuss the study further. If the child and their parents were keen to take part, the child was enrolled into the study. Each parent and the child (where appropriate) was asked to sign a consent form, and a photocopy of the form was given to the participants to keep.

For many of the children enrolled, management of their CF was shared with a local district general hospital (DGH). The appropriate local paediatricians were informed of the child's enrolment into the study and information about it, including the lead researcher's contact details, was sent to them.

Methods

Study design

Crossover versus parallel trial

The aim of this study was to compare the effectiveness of daily rhDNase with alternate-day rhDNase and HS in the treatment of children with CF. The usual way of comparing different therapeutic measures is a randomised controlled trial. Two designs of randomised controlled trials were considered: parallel and crossover. In a parallel design, one group receives the test treatment, and one group the control. Participants must be selected so that the baseline characteristics of the groups are matched. In a

crossover trial each participant is given each treatment in turn; this design is suitable for investigating an underlying disease which is incurable. Fewer patients are required in a crossover compared with a parallel group trial to achieve the same statistical power. Each patient acts as his or her own control which eliminates the need to match study groups.

However, there are disadvantages to the crossover design. First, there is the problem of participants who discontinue their treatment before the trial is complete. This also causes analytical difficulties in parallel group trials, but at least useful information may be gained up to the time of discontinuation. In crossover trials this is extremely difficult to obtain, and the patient can provide no direct information about any treatments they do not receive.

There is also the problem of interaction between treatment and duration of treatment, which occurs if the effect of treatment is not constant over time. If it is likely that the length of time for which a treatment is given modifies the effect of that treatment, the results of the crossover trial will be difficult to interpret. For example there might be a physical persistence of the drug or the drug might be disease-modifying. These are both examples of carry-over, which is the persistence, whether physically or in terms of effect, of a treatment applied in one period into a subsequent period of treatment. In the former case there is the danger of a drug interaction, and in the latter the second treatment may appear to benefit the patients when in fact the previous treatment is responsible. These types of carry-over would bias the estimates of the effect of treatment. Alternatively, during the time in which the crossover trial is run, the condition of the patients might markedly deteriorate (e.g. in adults with CF) or suffer a secular change (e.g. due to seasonal variation). The benefit of the test drug might be dependent on the current state of the patient. To some extent, randomising the order of treatments may overcome some of these problems.

Finally, there is the problem of inconvenience to patients. In crossover studies the patients may be asked to trial several treatments and the total time they spend under observation may be longer. This can be turned into an advantage as it gives a patient the opportunity to try out different treatments and make an informed choice.

A parallel design is the ideal choice for a therapeutic trial in which three treatments (that is, daily rhDNase, alternate-day rhDNase and HS) are being studied. There is no concern about interaction between treatment and duration of treatment. However, a far greater number of patients is required and the study groups need to be matched. This is often difficult in patients with a variable disease such as CF.

Power calculation

The FEV_1 measure was chosen as the primary outcome of the study (see discussion below). Given an FEV_1 within-subject standard deviation (SD) of 0.13 litres in children with CF,[88] a trial of 40 patients per group would have a power of more than 90% to detect, as significant at the 5% level, an average difference between any two treatments of 0.1 litres in the final FEV_1 measurements. Therefore a parallel trial design would need to ensure that at least 40 patients were allocated to each treatment group. For individual patients, a significant change in lung function due to each treatment would be a change in FEV_1 of at least 10%, based on the study of Fuchs and colleagues.[15]

A parallel trial would therefore have required a total of 120 evaluable patients with 40 patients in each of the three study groups (daily rhDNase, alternate-day rhDNase and HS). In all probability, recruitment of more patients would have been needed, to allow for drop-outs. As mentioned above, the study was undertaken at two large CF centres in London (Great Ormond Street Hospital and the Royal Brompton and Harefield Hospital), and after application of the inclusion criteria, there were only 62 eligible patients from these two study centres. Other centres were not participating in the study, as we needed to ensure reasonable consistency of treatment policies for all the patients involved and good quality control for assessing outcomes measurements between the centres. Furthermore, if only 62 patients were eligible from these two large CF centres, many more smaller centres would have been needed to significantly increase the number of suitable patients. A crossover trial would require only 40 evaluable patients, and we therefore chose that study design. Our aim was to recruit 50 children to allow for withdrawals from the trial.

Other trial considerations

Blinding

A double-blind design is ideal, but previous studies have shown that blinding for HS is virtually impossible.[63,64] It can easily be distinguished from rhDNase by its salty taste and timing of administration in relation to CPT. Even in trials comparing HS with IS, HS was easily identified by particpants

because of its stronger taste.[63] An attempts to mask the taste of HS by adding a reagent such as quinine was considered; however this would not affect the timing of HS treatment, which has to be given immediately prior to CPT, whereas rhDNase is administered at least 1 hour before CPT (see discussion below). Blinding is also difficult with rhDNase, as it effervesces when it is placed in the nebuliser cup. The trial was therefore open-label, with both the patient and clinician being aware of which treatment was being taken.

Study duration

The duration of the study needed to be long enough to show a sustained treatment effect. Many patients initially have a dramatic improvement in lung function with rhDNase which declines after the first month.[15] A long treatment period would also be more reliable in demonstrating the effect of treatment on reducing the occurrence of pulmonary exacerbations. However if each treatment duration was too long, this could affect adherence and motivation to remain in the study, as each patient was required to take all three treatments. There also needed to be a washout period between each treatment period which would increase the trial duration further.

Response to rhDNase at 12 weeks has been shown to be a good predictor of response at 1 year.[24] It was therefore decided that each treatment should be given for 12 weeks.

Washout period

During the study each patient was to receive daily rhDNase, alternate-day rhDNase and HS for 12 weeks each, in a randomised order. It was important that carry-over of one treatment into subsequent treatment periods should be prevented. This was addressed by having a washout period; it is believed that the effect of the treatment given previously disappears during such periods. During the washout period no nebulised mucolytic drug was to be administered (passive washout).

If the washout period had been too long this would have prolonged the duration of the study with consequent adherence problems. Furthermore, asking patients to remain at a potentially lower level of respiratory function for several weeks would not have been ethical or practical as it would have caused concern for the patients and their parents. Therefore the duration of the washout period had to satisfy the contradictory needs of ensuring no carry-over and the practical and ethical constraints of the treatment of the children. Previous studies have shown that 2 weeks is a sufficient time for a complete washout effect to occur for both HS[63] and rhDNase,[13] so this length of time was chosen.

Trial drugs

Recombinant human deoxyribonuclease

The dosage of rhDNase was 2.5 mg nebulised, either once a day or once every other day depending on which limb of the trial the patient was undertaking. Patients were instructed to administer rhDNase at the same time each day and at least 1 hour before CPT.[20] The drug comes in plastic vials containing 2.5 mg (i.e. one dose) from which the drug is squeezed into the nebuliser cup, and the rhDNase was prescribed at the patient's hospital or by their general practitioner (GP).

Hypertonic saline

Various concentrations of HS have been used in the past. Robinson and colleagues[61] showed that 12% HS caused a greater increase in mucociliary clearance than 3% HS. They demonstrated no difference between 7% and 12% HS, but several patients complained of irritation at the back of their throat when using the 12% HS solution.[61] Most studies, therefore have used a concentration of 5 to 7%. The volume of HS to be nebulised has varied in previous studies from 4 to 10 ml.[63,89] The time taken to deliver a nebulised drug is likely to be important for patient adherence. Patients will generally not accept long delivery times, especially if the treatment is required several times a day.[90] In a recent short-term study,[64] it was found that 10 ml of 5.85% HS nebulised twice a day took about 84 minutes to administer. This long inhalation time was unacceptable, and the authors suggested that if this regime was instituted as permanent therapy there would be problems with adherence. The maximal time for nebulisation is generally believed to be 5 to 10 minutes. In their study, Riedler and colleagues[62] used 6% HS nebulised for 10 minutes; there was improvement in sputum expectoration, and the patients perceived better quality of CPT.

For our study, we wanted to use the maximum tolerable concentration of HS. In a preliminary study, several members of the Great Ormond Street Hospital CF team were given nebulised HS at concentrations varying from 3% to 12%. It was found that 12% was too salty, whereas 3% could hardly be tasted; 7% was found to be the maximum concentration acceptable. Also, 7% HS was cheap, commercially available, and was occasionally used at the Royal Brompton and Harefield

Hospital by physiotherapists to aid airway clearance in CF patients admitted to hospital. A volume of 5 ml of 7% HS took about 10 minutes to nebulise and this dosage was therefore selected.

Due to its rapid onset of action, nebulised HS has been used immediately before CPT, twice a day, in previous studies,[63,64] and so in our study 5 ml of 7% HS was nebulised twice a day prior to CPT. HS was prescribed by the study centre at the beginning of the treatment period. It is provided in 100-ml bottles, and each patient was shown how to draw up 5 ml of HS (one dose) by syringe and place it in the nebuliser cup. As each bottle contained 20 doses of HS, the patients were given ten bottles, 20 syringes and 20 needles for the duration of the treatment. Each syringe and needle could be used for up to 1 week.

Nebuliser system

Choice of system

The choice of nebuliser could influence clinical efficacy.[91] The therapeutic effect of a nebulised drug depends on the actual dose that is deposited in the lower airways and the pattern of distribution (central versus peripheral airways). Three output characteristics (efficiency, respirable fraction and delivery) of the systems need to be evaluated. The efficiency of a nebuliser system refers to the fraction of the dose of drug placed in the nebuliser cup that reaches the mouthpiece, because a certain volume of unused drug or dead space always remains in the nebuliser. With regard to the respirable fraction, the size distribution of the aerosol droplets is an important parameter affecting eventual deposition in the lower airway.[92,93] In the upper airway, where the velocity of inhaled air is the greatest, larger particles (more than 5 microns in diameter) are removed by impaction in the nasopharynx or oropharynx. Some droplets of less than 0.5 microns in diameter may deposit by diffusion in the alveolar region and throughout the airway, but many are exhaled. Particles between 1 and 5 microns in diameter have the highest chance of reaching and depositing in the lower airways, either by impaction at branch points or by sedimentation as airflow slows in the peripheral lung.[94] The particles in this range are called the respirable fraction, and the mass of the drug contained in these droplets is the respirable mass. The delivery of the nebuliser is the product of efficiency and respirable mass.

At present two main varieties of nebuliser are available: the jet and the ultrasonic types. Jet nebulisers consist of a nebuliser cup, in which the drug is placed, which is attached to an electrical compressor. The aerosol is generated from a flow of gas from the compressor. The gas passes through a very small hole (the jet or Venturi) resulting in liquid being sucked up through the small hole from the cup base and atomised. The resulting large particles then impact upon baffles to generate small respirable particles.[95] Ultrasonic nebulisers are electrically driven systems in which a rapidly vibrating piezoelectric crystal vibrates the drug solution and produces aerosol particles of a respirable size.[95] Both types of nebulisers have been used in studies of HS in CF.[62–64] However only jet nebulisers are recommended for use with rhDNase,[20] as the energy from the crystal in ultrasonic nebulisers may heat or disrupt the sensitive protein. Ultrasonic nebulisers are also less robust than jet nebuliser systems and are generally not used for domiciliary therapy in CF. In the two CF centres involved in the study, patients were using jet nebulisers. No patient had an ultrasonic nebuliser at home or knew how to use one. A jet nebuliser was therefore used to administer the trial drugs.

The CF patients at both centres were using various combinations of nebuliser cups and compressors to nebulise rhDNase, antibiotics and bronchodilators. Most, however, were using the Durable Sidestream™ nebuliser with a Porta-Neb™ compressor (both Medic-Aid, UK). This is a recommended combination for administering rhDNase. The Porta-Neb is an updated version of the CR50 compressor, which is no longer produced. The Porta-Neb delivers a flow rate of 6.5 l/minute. The Durable Sidestream boosts the flow rate to 16 l/minute with its Venturi system. The combination delivers a mass median aerodynamic diameter (MMAD) of 3 microns, with 80% of the output volume within the respirable range. It can deliver a volume of 2.5 ml in less than 6 minutes.

Shah and colleagues[96] have compared the delivery of rhDNase by the Durable Sidestream and CR50 compressor with that of the Hudson T Up-Draft II™ and Pulmo-aide™ compressor, which have been used in previous rhDNase trials.[15,17] The systems differed in their delivery characteristics. The Sidestream nebuliser had a faster nebulisation rate ($p < 0.05$), lower MMAD ($p < 0.001$), and higher percentage of particles in the respirable range ($p < 0.001$).[96] No statistically significant difference in patient response was seen between the two systems, but a trend toward a greater improvement in FEV_1 was seen in the group using the aerosol producing smaller particles (16% versus 11.4%, $p = 0.14$). Another study[97]

also assessed lung function responses to rhDNase, delivered by two nebuliser systems, in CF patients with mild lung disease (FVC of 70% or greater of predicted value). Here, also, a trend to greater improvement as measured by FEV_1 was found with the smaller-particle system ($p = 0.06$).

The HaloLite™ (Medic-Aid) is a relatively new nebuliser system which is considered to allow more precise assessment of drug delivery patterns and adherence to treatment. This system incorporates adaptive aerosol delivery: for each patient, the key breathing parameters with regard to targeting aerosol delivery (flow, frequency, inspiratory time) are monitored in order to determine the aerosol pulse time. Aerosol is delivered during the first 50% of each inhalation, and the system continues to adapt throughout the treatment. This ensures precise dose delivery to each patient, independently of their breathing pattern. The HaloLite also incorporates a patient logging system. This records the date, time and dose received for each treatment, which allows objective measures of adherence to be made. However, at the start of our study, there was insufficient evidence on the use of HaloLite in delivering rhDNase and HS.

The Durable Sidestream nebuliser with a Porta-Neb compressor was chosen in this trial. Each patient was supplied with a new Porta-Neb. The Durable Sidestream nebuliser can last up to a year with regular cleaning. However, to avoid potential deterioration in performance later on in the study, each patient received a new Durable Sidestream at the beginning of each treatment period.

Use of the nebuliser system

The patients and parents were shown how to use and maintain the nebuliser system.

It has been demonstrated that the respiratory variables of patients, including inspiratory flow rate, respiratory rate, breath-holding time and tidal volume, are as important as aerosol variables in determining the site of aerosol deposition.[98] Avoidance of a high inspiratory flow rate (> 30 l/minute) improves lower airway deposition by reducing upper airway impaction.[99] Ilowite and colleagues[100] demonstrated that the maximum aerosol deposition with a jet nebuliser run at 9 l/minute occurred with a minute ventilation of 12 l/minute, with reduced deposition at the extremes of minute ventilation. While increased dwell time of an aerosol allows for settling in the airway, this is offset by the waste of aerosol from a constant-flow nebuliser during breath-holding or exhalation. Therefore, the patients were recommended to breathe in and out through their mouth whilst nebulising the medication, and to occasionally take a deeper breath in. If for any reason they needed to take a break (e.g. to cough), they were advised to switch off the compressor to ensure that no drug was wasted. The nebuliser should then be restarted as soon as possible. The patients were given a diary card in which these guidelines were stated, and also emergency contact telephone numbers.

Study procedure

Clearly it was important to compare treatment effects with a baseline which was as stable as possible. In order to ensure that patients were clinically stable at enrolment, they had to have been free of any lower RTI requiring a change in antibiotics, steroids or bronchodilator treatment during the 14 days before randomisation. This definition of clinical stability has been used in previous rhDNase trials.[14,15] Furthermore, following randomisation many patients would discontinue their current mucolytic treatment, and this might cause a deterioration in respiratory function; thus discontinuation would have been unethical in patients who were already clinically unstable.

Patients were interviewed by telephone to ensure that they met entry criteria. If they did not, randomisation was delayed. When they were clinically stable, patients were randomly allocated to a treatment order and were seen 2 weeks later to start the first treatment. Randomisation, which was done over the telephone by an independent trials coordinating unit, was stratified by hospital and balanced after each group of 12 children. Block randomisation was used so that each of the six possible treatment orders was equally distributed within the study group, to remove any effects of treatment order and season. Patients who were on rhDNase or HS prior to the study discontinued the treatment for at least 2 weeks before attending their first visit.

Patients were seen at their CF centre for the study visits. There were six visits in total, occurring at the beginning and end of each treatment period (*Figure 1*). Patients and their parents were phoned 1 week and then 6 weeks after the start of each treatment period to ensure that there were no concerns and to maintain adherence. At each visit, the lead researcher reviewed the patients. Two respiratory function technicians and two CF nurses supervised outcome measurements at Great Ormond Street Hospital and the Royal Brompton and Harefield Hospital, respectively.

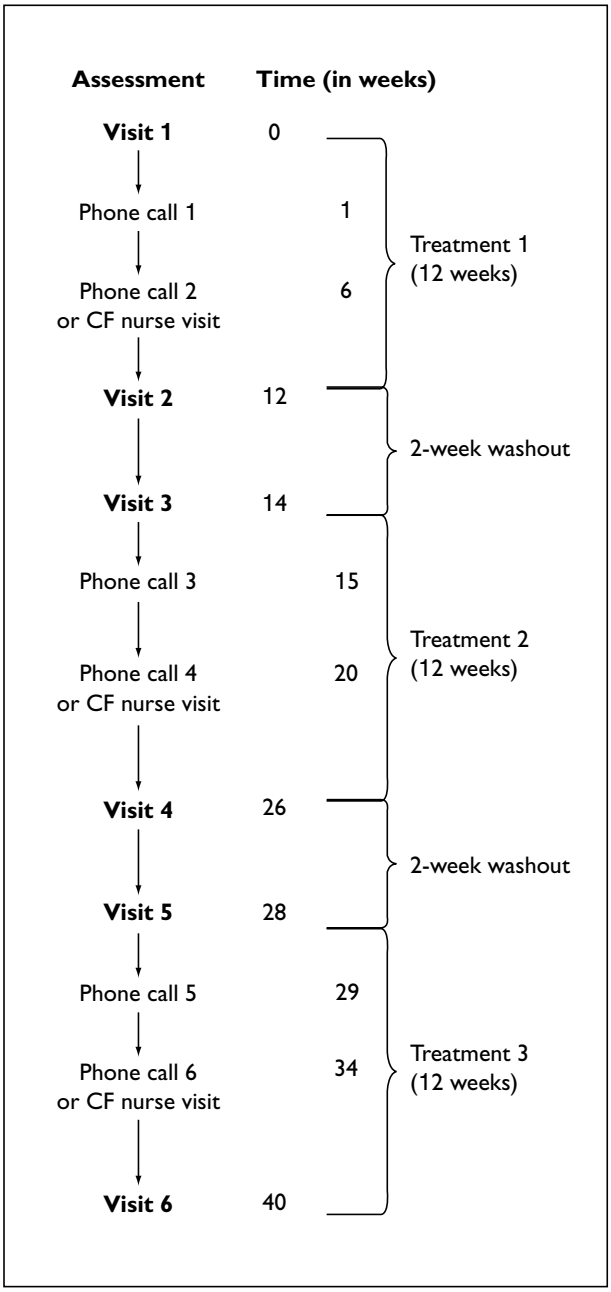

FIGURE 1 *Study procedure*

They used set protocols for measuring each outcome and their technique was assessed to maintain reproducibility.

The duration of each treatment period was 12 weeks. If the patient was unable to make visit 2, 4 or 6 (see *Figure 1*) on the allocated day, they could be seen within a 2-week period before or after that day. Between the end of one treatment and the start of the next, there was a washout period when no nebulised mucolytic drug was administered. However if patients were unable to attend after a 2-week washout, the period could be extended to a maximum of 4 weeks.

Airway response to HS

Before a patient began 12 weeks of HS therapy, it was important to formally assess airway response to HS. In previous studies of HS in CF,[62,63] all the patients have been given an inhaled SAB prior to HS to prevent bronchoconstriction. However, Rodwell and colleagues[67] have demonstrated that there is a group of CF patients who do not develop sustained bronchoconstriction with HS and therefore do not require premedication with an SAB.

At the study visit at which HS treatment was to be commenced, all patients were given a test dose of HS to assess airway response. First, the FEV_1 value, measured by spirometry in accordance with American Thoracic Society guidelines[101] (discussed below), was recorded in all patients. Then, if the patient was using an SAB, this was taken 10 minutes before the HS dose. The FEV_1 was then measured in all patients 15 minutes after HS had been administered.

If there was a drop in FEV_1 of more than 15% (severe bronchospasm) after HS in a patient who had used an SAB, that patient was deemed ineligible for HS treatment. According to the study protocol, those patients not using SABs and who had a drop in FEV_1 of more than 15% were to be asked to return the following day for a repeat HS test dose with prior inhalation of an SAB. If, despite use of the SAB there was still a drop in FEV_1 of greater than 15%, the patient was to be regarded as ineligible for HS treatment.

However, patients were still able to have the other two treatments (alternate-day and daily rhDNase), and their subsequent treatments were each brought forward one period.

Criteria for modifying the study procedure

If the patient was unwell at the time of visits 2, 4 or 6 and their clinician felt that stopping the nebulised drug was inadvisable at that point, the patient would have their study visit but the drug would be continued. Once the patient had recovered from the illness, the nebulised treatment was discontinued and the washout period began. This was recorded in the patient's folder. At each visit and 6 weeks into each treatment period, patients were specifically asked about the occurrence of any adverse events. These were recorded along with details of duration, severity and action taken. If the adverse event was thought to be related to the study medication and if any change to the study

medication was undertaken, this was also noted. The decision to withdraw a patient from the study was made by the patient's clinician following discussion with the respiratory consultants from the study centres.

If the patient had an RTI at the time of visit 2, 4 or 6, they were still advised to be seen by the clinician and to have the study visit. If this was not possible because the patient was either too unwell or had been admitted to their local hospital, then the patient was seen at the next possible time. This was recorded in the patient's study folder. The nebulised treatment was discontinued only when the patient had recovered from the RTI; the 2-week washout period would then begin.

If the patient required antibiotics or had a change in treatment during a washout period, this was noted in the patient folder. However, they nevertheless started the next treatment period on the allocated day (i.e. 2 weeks after completing the previous nebulised treatment). If the patient required nebulised mucolytic treatment during the washout period, the study medication which had just been discontinued would be given. Once the patient had recovered from the RTI, then this mucolytic was discontinued and the 2-week washout period would begin again from the beginning.

Whenever it was not possible to see a patient at the allocated time, this was noted in the patient folder along with the reason.

Monitoring of adherence

Background

The daily management of CF involves a complex time-consuming range of treatments and self-care. Adherence to treatment may be an important factor in the successful management of the disease. However, clinical experience indicates that complete adherence is very unusual. (The terms adherence and non-adherence are used in preference to compliance and non-compliance. The latter terms imply coercion, in contrast to the cooperation that is desirable.) We need to know more about adherence in order to try to improve it. Demographic factors (age, sex, knowledge of disease) and clinical factors (disease severity, age at diagnosis, frequency of clinic visits) have been evaluated as possible predictors of adherence in CF, with equivocal results.[102–104]

There are many reasons for non-adherence. Koocher and colleagues[105] have classified non-adherence in CF into three main types: inadequate knowledge, psychosocial resistance and educated non-adherence. Inadequate knowledge implies that lack of available information is the main reason for non-adherence. In psychosocial resistance, issues such as control struggles with parents, peer group pressures and striving for normality are paramount. Educated non-adherence involves conflicts and difficult choices, based on a full understanding of both the reasons for the prescribed regime and the results of not following it.

As yet there are no conclusive data linking poor treatment adherence and progressive disease in CF. However, it is commonly assumed that the consequences of poor adherence are infective exacerbations, disease progression, the costs of wasted drugs, increased hospitalisation and erroneous conclusions about the efficacy of treatment. In the present study, comparisons between the trial drugs would not be valid if the patients did not take them. Therefore it was important to assess the adherence to treatment.

Different methods have been used to evaluate adherence in clinical practice and trials, each having advantages and disadvantages. The use of electronic monitoring devices is probably the most accurate approach, and would have been the ideal way to determine how often and for how long the nebulised treatments were being administered. However, the electronic devices, which would have been attached to the nebuliser, are expensive and their cost could not be covered by the funding available for the study. There is also a risk that the electronic device itself may introduce bias if it alters the appearance and functionality of the nebuliser.

Other methods of monitoring adherence were therefore assessed. The simplest method is patient self-reporting, which is easy for the patient to perform but is sometimes inaccurate and may provide an overestimate of adherence. These overestimates may reflect patient forgetfulness, a bias toward remembering adherent days rather than non-adherent days, or a desire to please the clinician. The validity and reliability of self-report measures can be enhanced by diminishing the social pressure on patients to under-report non-adherence by phrasing adherence questions in a non-threatening manner and assuring them that responses are confidential.[106] Self-report questionnaires have been validated by comparing adherence with tablet-count[107] and clinical outcome measures.[108] Thus, although self-reporting does not provide an exact measure of when and how patients took their medication, it may be used

to grade patients according to their relative standing on the adherence dimension.[109]

The accuracy of clinicians' impressions of adherence has been shown to vary widely in chronic disease. When relying on clinical intuition, physicians generally overestimate the degree to which their patients comply with their directives, and often fail to recognise the non-adherent patient.[110] Similarly to self-reporting, the use of written diary cards for patients to record their symptoms or peak flow (in asthmatic patients) may be used to assess adherence. However, this method may be inaccurate as a result of copying errors or mistimed entries, and adherence may be overestimated because of deliberate retrospective false entries made by patients in order to please the clinician.[111,112] Studies have shown that the best adherence is obtained during the first 2 weeks, with a progressive diminution thereafter and an increasing number of invented values.[113,114]

Pill-counting is a more objective means of assessment; however, it is only of limited value where there is intentional non-adherence because it does not distinguish between correct use of the drug and the deliberate discarding of medication prior to a scheduled visit to the doctor or clinic (drug 'dumping'). Similar problems exist with medication-monitoring devices, such as microprocessor-based pill dispensers or recorders attached to nebuliser systems. Furthermore, a record of the correct number of tablets or nebulised doses at the appropriate time does not necessarily indicate that the patient is taking the medication correctly.

Measurement protocol for adherence

In our study, adherence to treatment was monitored in two ways. Patients were asked to return all unused bottles of HS and used vials of rhDNase. From this, the percentage of prescribed doses that could have been taken could be calculated. In addition to this, each patient recorded the treatment doses taken for each trial drug in their patient diary. Patients were telephoned at 1 and 6 weeks into each treatment period to enhance adherence.

Outcome measures

The benefit of each of the three treatments needed to be assessed and compared. For individuals with CF, this benefit ideally would be increased survival time. However, as discussed earlier, survival time is an impractical measure of clinical efficacy. Therefore outcome measures acting as surrogate markers of increased survival time were used, as well as measures of more immediate improvement such as QoL assessments.

A number of other measures, such as exhaled nitric oxide levels, were considered for use as outcome indicators. However, there had to be a balance between the number of measured outcomes and the duration of each study visit. Each patient was seen at the study centre six times and for some the journey time from home to the study centre was up to 2 hours. It was therefore important that the visit should not be longer than 1 hour: otherwise the patients were likely to get bored, which could have affected willingness to continue with the trial and adversely impacted on the quality of the measurements made. Only the outcome measures that were thought to be essential in making a comparison between the treatments were included. These were based on the findings of the 1992 Consensus Conference sponsored by the CF Foundation, which assessed how to improve the definition of clinical outcomes for evaluation of new CF therapies.[83]

The primary end-point was change from baseline in FEV_1 value. Secondary end-point measures were FVC, number of pulmonary exacerbations, weight gain, exercise tolerance, QoL, total healthcare cost and cost-effectiveness. Each participant had a separate folder in which outcome measures were recorded.

Lung function

Background

Measurement of FEV_1 by spirometry is quick and easy to perform with most children over the age of 5 years and is routine at clinic visits. Although children with CF have increased within-patient variability for lung function measurements compared with healthy individuals,[88,115] this variability is not affected by the severity of pulmonary disease.[88] Most previous studies of rhDNase in CF,[14,15,17] have therefore used FEV_1 as the primary outcome. Studies have shown a relationship between FEV_1 and mortality in patients with CF.[45,116,117]

Change in FEV_1 was chosen as the primary outcome of the study. It was also important to study other measures of lung function. The forced expiratory flow rate between 25% and 75% of FVC ($FEF_{25–75}$) and mid-expiratory flow at 75% of FVC (MEF_{25}) are possible measures of small airways disease. However, they have much greater intra-subject variability than FEV_1.[115,118] FVC has a coefficient of variation similar to that of FEV_1, of 5% in normal individuals, rising to 10% in CF patients.[115] For flow at low lung volumes,

coefficients of variation of up to 30% are common.[115] Therefore only FVC was assessed as a secondary outcome.

Measurement protocol
The patients underwent spirometry which was done using a compact spirometer (Vitalograph, UK) in accordance with American Thoracic Society guidelines.[101] The spirometer was calibrated daily using a calibrated syringe up to a volume of at least 3 litres. Patients were asked to not to use SABs for at least 4 hours prior to testing to avoid an effect on lung function measurements. The time that the patient had last taken an SAB was recorded.

Three acceptable spirometry manoeuvres were performed.[101] From these, the largest FEV_1 and the second largest FEV_1 had to be within 0.2 litres of each other, and the largest FVC and the second largest FVC also had to be within 0.2 litres. The manoeuvre could be repeated a maximum of eight times until these criteria were met. The printouts from all the manoeuvres were kept. The largest FEV_1 and the largest FVC were recorded after examining the data from all of the acceptable curves, even if they did not come from the same curve.

On subsequent clinic visits, lung function was recorded within 3 hours of the time of day of the baseline reading. CPT may alter lung function in CF in the short term,[119] possibly by redistribution of sputum resulting in alteration of air trapping, or by inducing bronchospasm in those with hyper-reactivity. Patients were having CPT at the same time of day, so the timing of spirometry in relation to CPT remained consistent for individuals.

Pulmonary exacerbations
Background
Pulmonary exacerbations cause progressive lung damage in CF, affect QoL and lead to substantial health service resource use and costs. Reduction in pulmonary exacerbations has therefore been used as an outcome when testing the long-term effect of new respiratory drugs. In this study, an established protocol defining RTI was used.[15] A pulmonary exacerbation was said to have occurred when a patient was treated with parenteral antibiotics for any four of the following 12 signs and symptoms: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change found in physical examination of the chest; decrease in pulmonary function by 10% or more from a previously recorded value, or radiographic changes indicative of pulmonary infection.

Measurement protocol
The patient and parents were asked to record changes in symptoms, use of antibiotics and admissions to hospital, in patient diaries which were given to them. At the end of each 12-week treatment period, the occurrence of the above signs and symptoms was assessed to determine the number of pulmonary exacerbations that had occurred. Further information was obtained from the hospitals where patients had been seen.

Weight gain
Background
Growth failure and malnutrition are common clinical features in children with CF.[2,120–122] They are due to chronic negative energy balance caused by decreased caloric intake, increased energy loss, increased energy expenditure, or some combination of these factors.[123] These features are associated with pulmonary morbidity and mortality,[116,124,125] but the nature of the association is not fully understood. Lung dysfunction may impinge on weight gain because of increasing energy expenditure for the work of breathing.[126,127]

Advantages of monitoring weight as an outcome measure include ease of observation, and low cost. However, disadvantages include the fact that confounding variables, such as dietary intake, the extent of gastrointestinal dysfunction (including pancreatic insufficiency), and adherence to digestive therapies, also play a role in determining weight outcomes. Monitoring weight may not be useful in short-term studies unless large changes are expected. Thus these measurements are more likely to be of value in longer-term assessment of interventions. Weight loss and curtailment of growth as a result of lung dysfunction are usually noted in CF patients who have moderate to severe disease and may be less sensitive indicators of early lung disease. However, it is worth observing weight to ensure that there is no unexpected weight loss.

Measurement protocol
The patients were weighed at each study visit. Weight was recorded with the patient wearing underwear only.[128] Standardisation and calibration of the weighing scales within each study centre was carried out every 6 months by the hospital's biomedical engineering department.

Exercise tolerance

Background

With the progression of lung disease, the patient's inability to keep up with the physical tasks of daily life and play represents a major impairment to their quality of life. Studies have shown that exercise test results relate to survival in CF.[129,130] Limitation in exercise capacity has been ascribed to deterioration in pulmonary function leading to a decreased ventilatory capacity, and also to malnutrition, which leads to a loss in muscle strength.[131,132] It is usually not possible to predict exercise tolerance from standard lung function measurements.[133,134] Assessment of fitness and exercise tolerance is a useful measure of the impact the disease is having on the patient, particularly when repeated over time,[135] and exercise tolerance has been suggested as an important outcome variable in CF intervention trials.[83]

There is currently no single ideal exercise test for CF patients and the choice of an appropriate test must be based on the specific question under consideration. For example, if muscle strength is of interest, then a strength measure, such as the maximum amount of weight liftable at one time would be applicable.[136] An anaerobic test, for example the Wingate test,[137] would be most appropriate for assessing anaerobic, supramaximal energy bursts. Traditional progressive cycle or treadmill tests are useful for measuring maximal workload and oxygen consumption.[138] They are also appropriate for assessing ventilatory and cardiac responses to progressively increasing workloads.

Maximal tests have been considered the gold standard. However, this type of challenge does not simulate children's daily activity;[139] it is also expensive, tiring for the patient and time-consuming. For these reasons, another exercise test was needed for this study. Several different approaches to evaluating exercise tolerance in CF patients were considered, including supramaximal 'sprint' tests[137] and various submaximal measures, including walk tests[140] and the 3-minute step test.[141] All these tests have been shown to have validity and reliability.

A question of interest in the study was how the trial drugs would affect the ability of the patient to perform real-life work. At present this is most suitably assessed using the walk tests[140] and the 3-minute step test.[141] These tests record the cost of work in terms of oxygenation and heart rate. The 3-minute step test was chosen for the study.[141] Balfour-Lynn and colleagues[141] have shown this test to be tolerable for 91% of their CF patients and to be a reliable and reproducible way of increasing heart rate and breathlessness over resting values, as well as decreasing oxygen saturation (Sa_{O_2}). They found similar, but smaller, increases in breathlessness and pulse rate and comparable changes in Sa_{O_2} with the 6-minute walk test. When the 3-minute step test was performed by children with CF before and after a course of intravenous antibiotics, there was a marked improvement in exercise tolerance.[142]

The advantages of the 3-minute step test are that it is quick, simple and does not depend on patient motivation as maximal tests do. It was important for the test to be relatively quick as we needed to keep each study visit as short as possible to maintain patient motivation. Compared with a cycle ergometer or treadmill, the 3-minute step test is also more representative of how well children can exert themselves as part of normal daily life.[139] Results should not vary with encouragement unlike those from walk tests, and the equipment is portable. However, it has some clear limitations. With a set step height, the workload varies depending on the subject's height (and weight). It does not measure maximal functional work capacity, or even a set, known, reproducible submaximal workload.

Breathlessness is an important and often distressing symptom in children with CF. It is defined as the subjective awareness of having difficulty breathing or feeling out of breath. It can be measured subjectively or objectively. The visual analogue scale (VAS)[143,144] and the modified Borg scale[145,146] are the main instruments used for subjectively quantifying breathlessness. With these measures patients indicate how breathless they feel, and in general similar scores are obtained by both methods.[147,148] The VAS consists of a 10-cm horizontal line with two anchor points, one at each end. The left point (zero) is labelled 'not at all short of breath', while the other end (10 cm) is labelled 'the most breathless I have ever felt'. Patients put a mark through the line at the point where they think their breathlessness fits on this scale; this is then measured (in cm) from the zero point. The VAS was used in the study because, in practice, use of the Borg scale is problematic in many children, due to their difficulties in understanding some of the terms (such as moderate or maximal).[148]

One of the problems with subjective measurements is that the intensity of breathlessness does not necessarily reflect the degree of physiological alteration in cardiolpulmonary function that can

be measured. An objective score is useful as it gives an indication of how breathless the patient actually is. The objective measure of breathlessness used was the '15-count breathlessness score' (FCS) which has been validated for use in children with CF. To measure this, the patient is asked to take a deep breath in and count out loud to 15, in a period of 8 seconds. The number of breaths required to complete the count within this time, including the initial breath, is the score (thus, the minimum score is 1).

Measurement protocol
At each study visit, after resting from performing spirometry manoeuvres, patients underwent the step test. The test was explained to the patient and they were informed that they could stop the test at any time if they felt unable to continue. If the test was being performed for the first time, the patient was asked to practise the rhythm and timing of stepping prior to testing. They were also shown how to change the lead leg whilst stepping (i.e. the leg placed first on the step).

An SaO_2 probe, connected to a Biox 3700 pulse oximeter (Ohmeda, USA), was attached to the patient's finger and the lead was taped to the forearm to ensure minimal trace interference during stepping. Baseline values for resting SaO_2 and pulse rate were recorded from the pulse oximeter. Patients stepped up to and down from a single 15-cm aerobic step at 30 steps per minute for 3 minutes (regulated by a metronome). SaO_2 and pulse rate were recorded continually during the three minutes of testing. Standard encouragement was given at 1, 1.5 and 2 minutes into the test; this encouragement stated how far into the test the patient was (e.g. halfway through) and that they were doing well. The lowest value of SaO_2 and the highest value of pulse rate during the test were recorded. It was important to ensure that there was an adequate signal and trace from the monitor when these values were recorded. The test was stopped if the SaO_2 fell below 75%, if the patient was unduly breathless or struggling to keep pace and rhythm, or if the patient wanted to stop for any other reason. If the patient ceased stepping within the 3 minutes, the reason for cessation was recorded. Patients performed the FCS and VAS tests immediately before and after the step test at each study visit. The FCS test was always done first followed by recording of the VAS.

Quality of life
Background
Although lung function and exercise tests are outcome measures that can be monitored over time and with various interventions,[149] they do not evaluate the impact of CF on the patient's overall health status and level of daily functioning. For instance, they do not take into account other pulmonary and non-pulmonary problems associated with the disease or its treatment. Measures of QoL provide information about the impact of an illness and its treatment that may be more meaningful to patients with CF and their families than other conventional outcome evaluations. The goals of QoL measures include differentiation between people who have a better QoL and those who have a worse QoL and measuring how much QoL has changed over time.

In a review of outcome measures for clinical trials in patients with CF, the Consensus Group recommended that QoL measures be incorporated into Phase III clinical trials for children with CF.[83] However, when our study was designed there was no CF-specific QoL measure available. Instead, a general QoL measure which had been validated for CF patients had to be used. QoL is typically asessed by having the patient or parent complete a questionnaire. Three major types of QoL evaluations have been developed: health profiles, disease-specific instruments and utility measures.

Health profiles are generic instruments that assess important dimensions of health-related QoL (HRQoL) for a wide range of disease states. Their items are general and broad-based as they are designed for use with a variety of populations. The advantages of health profiles are their quick and easy administration and their generation of different scores for different domains (e.g. energy, emotional reactions and social isolation). Several health profiles have been developed, including the Nottingham Health Profile which has been used in several studies[150,151] to assess QoL in patients with CF. However several concerns about health profiles have arisen. As they must be applicable to a variety of diseases, they may not measure important dimensions of functioning for any one condition. They may also measure aspects that may be irrelevant to the condition of interest, and may not be responsive to small but important changes resulting from a clinical intervention. Furthermore, few health profiles have been developed and validated for use with children and adolescents.

Disease-specific measures of QoL are designed to assess the symptoms and areas of functioning that are most important to patients with a particular disease. They provide information that is maximally relevant to the clinician, and are sensitive

to the small but important changes in QoL that result from new treatments. At the time of our study, the work of Henry and colleagues[152,153] represented the only published effort to develop disease-specific measures for patients with CF. Substantial interest has been generated by this development of CF questionnaires, which have now been translated for use in Germany, Spain and the US. However, when our study was undertaken the US translation had not been published. The sensitivity of the CF questionnaires to changes in QoL is currently unknown and is being evaluated in longitudinal, clinical trials.

The utility model is derived from economic decision theory and is used to compare alternative treatments or assess the impact of different diseases. Utility measures yield a single value that reflects overall QoL. This approach has several strengths, including its weighting of societal preferences for various symptoms and functional states (e.g. general tiredness and limitations in major role activity) and its usefulness for generating data on the cost-effectiveness of clinical interventions. Limitations of this approach include uncertain applicability to children and adolescents, the absence of information on different aspects of QoL, and a potential lack of sensitivity to clinically meaningful changes in airway disease.

The Quality of Well-Being Scale

For the study, the Quality of Well-Being (QWB) Scale, which is the most widely used utility measure of QoL, was chosen.[154,155] It has been validated in several chronic diseases, including CF, arthritis and AIDS.[156] The QWB is a preference-weighted measure, combining three scales of functioning with a measure of symptoms and problems to produce a point-in-time expression of well-being that runs from 0 (for death) to 1.0 (for asymptomatic full function). The QWB has been used in the CF population in four studies.[154,155,157,158] In the initial study of Orenstein and colleagues,[154] the QWB was administered to 44 patients with CF, ranging in age from 7 to 36 years with an average FEV_1 of 66.5% of predicted value. Higher QWB scores were obtained by patients with better lung function and greater exercise tolerance. These data provided support for the validity of the QWB Scale in CF patients. Czyzewski and colleagues,[157] however, found that in adolescents with milder CF (mean FEV_1 of 81% of predicted value) QWB correlated less well with pulmonary function tests.

In the subsequent longitudinal study of Orenstein and colleagues, the sensitivity of the QWB score to changes in QoL following antibiotic treatment for a pulmonary exacerbation was examined.[155] In this case, respondents were directed to answer the questions on the QWB for the 3 days before and directly following treatment, and these scores were averaged. The majority of the 28 patients demonstrated improved pulmonary functioning and obtained higher QWB scores after 2 weeks of oral ciprofloxacin treatment. Furthermore, the changes in pulmonary function, other than for peak expiratory flow rate, were significantly correlated with the changes on the QWB Scale.

However, there are problems with the QWB Scale. It requires a trained interviewer, and is long and complex because it employs branching and probe questions. The questionnaire takes at least 20 minutes to complete. Therefore, for the present study the QWB Scale self-administered form 1.04 (QWB-SA UCSD Health Outcomes Assessment Program), which has been developed from the QWB, was used to assess QoL. The QWB-SA is comparable to the full QWB interviewer-administered questionnaire,[159] and takes less than 10 minutes to complete.

The QWB-SA questionnaire includes five sections. The first section asks about acute and chronic symptoms. However many of the symptoms specified are not applicable to children with CF, such as blindness and speech problems. Part I also asks about 25 acute physical symptoms (i.e. coughing or wheezing, shortness of breath) and 14 mental health symptoms (trouble falling asleep or staying asleep, spells of feeling upset). The format for these items requests respondents to think back over the last 3 days and indicate whether the symptom was present on no days, yesterday, 2 days ago, or 3 days ago (multiple responses are allowed). Part II uses a similar format and asks about self-care. It includes two items asking whether the respondent had been in an institution (hospital) and whether they needed help with self-care such as eating, dressing and getting around the home. Part III concerns mobility. Part IV considers physical activity and asks about physical functioning, such as walking or confinement to a bed or chair. Performance of usual activities, such as schoolwork, is evaluated in Part V. As with the QWB Scale, in the QWB-SA instrument any limitations and symptoms encountered by the patient yield point deductions from 1 (perfect health) that are weighted by preferences derived from large-scale population surveys.

Measurement protocol

The QWB-SA was filled in by the parents and patient together at each study visit.

Economic evaluation

Background

It has been increasingly recognised by policy-makers that cost-effectiveness is an important aspect of decision-making, when the objective is maximisation of population health as related to public health budgets.[160] This means that in addition to evidence on the relative effectiveness of competing interventions, information is also needed on the relative costs. The techniques of economic evaluation provide a framework for assessing the costs and effectiveness of different interventions.[161] The mean annual drug cost of daily rhDNase for CF patients has been estimated to be £7442.[39] However, apart from the drug cost, the effect of rhDNase on outcomes and on the total cost of care must be considered. It may be that improved outcomes following rhDNase, compared with placebo, may be associated with lower hospital costs.[40,41] The use of an economic evaluation technique, which emphasises the comparison of both outcomes and a broad range of costs, would seem particularly applicable to addressing the question of cost-effectiveness in this context.[161] Despite this, as discussed in chapter 1, there is a lack of detailed UK evidence on the cost-effectiveness of rhDNase therapy for patients with CF. There was therefore an apparent need to provide UK-based trial evidence on the relative costs and cost-effectiveness of rhDNase. As an integral part of the study we compared the costs and cost-effectiveness of daily rhDNase with HS and alternate-day rhDNase.

Methodology

The methodology used for the study followed recent general guidelines for economic evaluation,[162] and more specific recommendations for measuring costs in the course of randomised controlled trials.[163] This meant that resource use and unit costs were reported separately, requiring a detailed approach to resource use estimation. Unit costs were measured at several study sites, and the final cost estimates were compared between the study groups using stochastic measures of uncertainty in line with recent recommendations.[164,165]

Measurement of resource use

All healthcare resources used were assessed, including hospital contacts (inpatient, outpatient and day case), radiological investigations, blood tests, drug use, and the use of community services (including community nurse, physiotherapist and GP).

Patients were given a diary in which to record any contacts with health professionals and any changes in medications during the study. The diaries were filled in prospectively by the child and their parent together. These were then reviewed at the end of each treatment period. To confirm the accuracy of the diaries, further details were obtained from the patients' hospital notes, discharge letters and by contacting the supervising physicians and GPs. For each hospital admission, the duration of stay, reason for admission, health professionals involved, investigations, procedures and management were recorded.

The typical time input from different health professionals was recorded for each type of healthcare contact for patients with CF (appendix 1). This information was collected from the two postgraduate hospitals where patients were recruited for the trial. In addition, data were collected from a DGH to represent care provided by that type of hospital.

Unit costs

Unit costs, from the relevant departments at the two postgraduate hospitals and from the DGH, were collected at a suitable level for combination with the measures of resource use (appendix 2). The annual cost of employing each health professional, taken to be the midpoint of the salary scale for their grade (and including employers' costs and overtime payments but excluding London weighting allowance),[162] was divided by the number of hours worked, to give an average cost per hour.

The costs of blood tests and other investigations were taken from the price charged by the relevant department to another NHS provider (the direct-access price). The finance departments at the three hospitals also provided information on the total costs of consumables and overheads on the ward or department where CF patients were treated for the year April 1999 to March 2000. The total costs were divided by the annual number of occupied bed-days, to give costs per occupied bed-day. Capital costs were not available from the finance departments concerned. These costs were therefore estimated from a secondary source.[166]

For outpatient and ward reviews, a similar methodology was used for collecting unit costs. Drug costs were taken from the *British National Formulary*,[39] and community care costs were found from the publication by Netten and colleagues.[167] The maximum duration of drug usage within each therapeutic category was measured for each patient during each treatment period. For each intervention the costs of the nebuliser pot and compressor were included. All costs were adjusted to 1999–2000 prices using the hospital and

community health services price index.[168] Total costs for each treatment period were calculated by multiplying each patient's resource use by the unit costs.

Cost-consequence analysis and cost-effectiveness analysis

The main aim of the trial was to compare the effect of daily rhDNase with HS and alternate-day rhDNase. To assess the relative costs of these strategies we therefore also compared the costs of the different approaches. The comparison of both the costs and the effectiveness of daily rhDNase with those of HS and alternate-day rhDNase therefore formed the cost-consequence analysis. In addition however, it was thought to be desirable to be able to compare the cost-effectiveness of all three treatment strategies. The cost-effectiveness analysis used the primary outcome measure from the trial (FEV_1). This measure was chosen in preference to measures of HRQoL, which would have been unlikely to be sensitive to change in treatment regimen over a 12-week period.

Cost-effectiveness analysis has traditionally used the incremental cost-effectiveness ratio (ICER) to measure the relative costs of different interventions compared with the relative effectiveness. However, there have been difficulties surrounding the measurement and interpretation of statistical uncertainty when the ICER is used. To avoid these problems, alternative measures of cost-effectiveness, including the cost-effectiveness acceptability curve (CEAC) and net benefit statistic, have been developed. This study used these techniques to estimate the relative cost-effectiveness of the different treatment options.

Statistical analysis

Analysis of outcome measures

All analyses were executed using Stata v.6.0. For the statistical analysis of the primary outcome measure, FEV_1, beginning-of-treatment log FEV_1 values were calculated for daily rhDNase (x_{DD}), alternate-day rhDNase (x_{AD}) and HS (x_{HS}); similarly, end-of-treatment log FEV_1 values were calculated for daily rhDNase (y_{DD}), alternate-day rhDNase (y_{AD}) and HS (y_{HS}). The baseline-adjusted effect of daily rhDNase as compared with HS is estimated as the intercept of a regression equation which has ($y_{DD} - y_{HS}$) as the response variable and ($x_{DD} - x_{HS}$) as the explanatory variable. A similar regression of ($y_{DD} - y_{AD}$) on ($x_{DD} - x_{AD}$) provided a baseline-adjusted estimate of the effect of daily versus alternate-day rhDNase. These intercepts have been transformed back to the original measurement scale (i.e. FEV_1, in litres) using the exponential function (the inverse of the natural logarithm). This transformation yields the estimated effect of daily rhDNase as a proportion of the effect of the comparison treatment. Both analyses were followed by an analysis of residuals to ensure normality of the distribution and homogeneity of variance across the range of fitted values.

These simple analyses were followed by a further linear regression analysis for each treatment comparison in which any confounding effects of different treatment periods, different seasons and the child's age were controlled. This was achieved by regressing log FEV_1 at the end of the treatment period on the linear combination of the following: treatment (one indicator term distinguishing daily rhDNase from the comparison treatment); log FEV_1 at the beginning of the treatment period; treatment period (two indicator terms distinguishing the second and third periods from the first); season (three indicator terms distinguishing April–June, July–September and October–December from January–March); age at the beginning of the treatment period, and disease severity as measured by the mean of the observed baseline percentage of predicted FEV_1 value. This model was fitted to the data using the generalised estimating equations (GEE) approach. As each child receives each treatment and we are basing the analysis on the differences in each child's subsequent outcomes, we will be making comparisons between correlated outcomes. To accommodate this, estimation of the correlation between the children's responses in the different treatment periods was included in the GEE analysis. This was done under the assumption that there would be an equal level of correlation between each pair of treatment periods. This correlation structure was estimated using a model fitted to the data for all three treatments, which additionally included the interactions between the effects of those different treatments and the other explanatory variables. The use of such an over-elaborate model to estimate the within-subject correlation reduces the risk of allowing those estimates to be inflated by the mistaken omission of important variables, such inflation potentially resulting in biased estimates of the treatment effect. The adequacy of the estimated correlation structure was confirmed by refitting the model with the less restrictive but less powerful 'independent correlation matrix'. In this case each element of the correlation matrix is estimated independently of the other elements.

The effect of disease severity on the relative effects of treatment on the primary outcome measure was investigated as the single subgroup analysis. Disease severity was measured as the mean of the percentage of predicted FEV_1 measurements taken at the beginning of all available treatment periods. The more complex analysis of the primary outcome described in the previous paragraph was extended to include the relevant interaction term. Two such models were estimated for each treatment comparison, one with disease severity included as a continuous variable, for conducting a significance test, and a second with disease severity included as a dichotomous variable (split at the median) to allow an easily interpretable estimation of the relative effects of treatment.

Statistical analyses of secondary outcome measures (other than pulmonary exacerbations and total costs) were conducted in a similar manner to the simple analysis of the primary outcome measure. The log transformation was not used for secondary outcome measures, and so baseline-adjusted treatment effects were estimated as the difference between daily rhDNase and the comparison treatment expressed in the units of measurement. The number of children who experienced one or more pulmonary exacerbations requiring intravenous antibiotics in a treatment period was compared between treatments using McNemar's test based on the exact binomial probability.

Analysis of costs and cost-effectiveness

The estimated mean difference in total healthcare costs was calculated for each of the two treatment comparisons. However, in order to understand why differences in cost between the interventions might exist, mean differences in resource use were reported (with 95% confidence intervals (CIs)). Due to skewed cost distributions, the 95% CIs around the mean total cost differences between the treatment periods were calculated using non-parametric bootstrapping techniques.[164]

Bootstrap techniques are based on taking multiple random subsamples (1001 were used here) of the participants in the study sample and recalculating the statistic of interest with the data from each subsample. The subsamples are of the same size as the original sample. They are obtained using the method of 'sampling with replacement', and so will omit some of the original sample due to other members being randomly sampled on two or more occasions. This re-sampling is intended to mirror the original sampling of the study participants from the population. The distribution of values obtained from the multiple calculations of the statistic of interest, provides an empirical estimate of the sampling distribution for that statistic. Non-parametric bootstrap techniques do this in a way that avoids making strong assumptions about the nature of that sampling distribution. The 95% CIs have been derived from the estimated sampling distribution by taking the 2.5th and 97.5th centile values as the lower and upper limits of the interval. They are interpreted in exactly the same way as CIs calculated using traditional algebraic techniques.

The aim of the cost-effectiveness analysis was to find the relative cost-effectiveness of the three different strategies, so that the 40 patients who had received each of the treatments were included. This approach differed from the trial analysis in which two separate pairwise comparisons, of daily rhDNase versus alternate-day rhDNase ($n = 43$), and of HS versus daily rhDNase ($n = 40$), were undertaken. All statistical analyses are based on comparisons between treatments as assessed from within-patient differences, since the trial used a crossover design.

For each treatment period the change in effectiveness was calculated by taking the natural logarithm of the end-of-treatment FEV_1 values, that is, y_D, y_A, and y_S, and beginning-of-treatment FEV_1 values x_D, x_A and x_S, for daily rhDNase, alternate-day rhDNase and HS, respectively. The difference in log FEV_1 values (e.g. $y_D - x_D$) was calculated for each treatment period, and compared between treatments. For example, the incremental effectiveness of daily versus alternate-day rhDNase, was:

$$E_{D-A} = (y_D - x_D) - (y_A - x_A)$$

This method of adjusting for the baseline differed from the original trial analysis, which used analysis of covariance. The incremental effectiveness was calculated on a log scale, which enabled the results to be interpreted in terms of percentage differences in FEV_1.

For each treatment comparison, the mean ICER was calculated by dividing the mean incremental cost by the mean incremental effectiveness, and corresponded to the additional average cost for a 1% improvement in FEV_1.

The non-parametric bootstrapping approach was used to plot the incremental costs and effects on the cost-effectiveness plane. The ceiling ratio, R_c, is defined as the amount that the healthcare decision maker is willing to pay. The CEAC shows the probability that the intervention is

cost-effective for various values of R_c. The CEAC was derived by plotting the proportion of the bootstrap samples which could be regarded as cost-effective, when the R_c was varied from £0 to £400 per 1% improvement in FEV_1.

The net benefit approach requires either the difference in costs or the difference in effects to be re-scaled using the R_c. Net benefits on the cost scale are defined as follows:

$$\text{Net benefits} = (R_c \times \text{difference in mean effect}) - \text{difference in mean cost}$$

Net benefits were calculated for each bootstrap sample for a range of R_cs from £100 to £400 per 1% increase in FEV_1. Mean net benefits were reported with 95% bootstrap CIs.

In the sensitivity analysis, the price of rhDNase was reduced from the *British National Formulary* price by 10–30% to assist with the generalisability of the results, since in practice healthcare providers may purchase rhDNase at a lower price. Similarly the effect of changing the cost per hospital day was assessed to examine the impact of cost variation between providers.

Chapter 3
Results

A total of 48 children were enrolled into the study, with eight children being randomly allocated to each of the six possible treatment orders. One 14-year-old girl dropped out of the study almost immediately, due to what became a prolonged illness. She is not included in the remainder of this analysis as little other information is available for her. Considering the remaining 47 children, recruitment was even between the two sites with 24 children being enrolled into the study at the Royal Brompton and Harefield Hospital and 23 being enrolled at Great Ormond Street Hospital. *Table 1* gives the demographic, anthropometric, and clinical characteristics of these children as observed at the baseline assessment.

Airway response to HS

Among the children, 45 underwent the HS test dose. The 35 patients who were using SABs as part of their normal treatment regime were given them prior to the HS test dose, according to the study protocol; 22 patients were taking terbutaline sulphate and 13 were having salbutamol. The dose of SAB varied from 500 µg to 1000 µg depending on the age of the patient. SAB was delivered either via a turbohaler or a metered-dose inhaler and spacer device. A total of 35 patients were on inhaled steroids.

A fall in FEV_1 with HS was found in 30 patients. The mean change in FEV_1 was –3% (range +25% to –22%). Three children were found to be ineligible for HS and did not participate in the HS treatment for this study. Two of the three children experienced a drop in FEV_1 which was greater than 15% (21% and 22%, respectively) despite using SABs. The third child refused to proceed with the test dose, reporting that HS made her breathless. A post-HS dose FEV_1 was not recorded for this patient. These three children were taking SABs regularly and took them prior to the dose of HS,

TABLE 1 *Characteristics of the study population at baseline (n = 47)*

	Mean (SD)	Range	*n*	%
Age, years	12.6 (2.8)	7.3 to 17.0		
Weight, kg	40.0 (12.6)	18.8 to 77.4		
Females			28	60
FEV_1, litres	1.18 (0.47)	0.44 to 2.34		
FEV_1, % of predicted	48 (15)	14 to 77		
FVC, % of predicted	68 (22)	20 to 112		
Change in oxygen saturation with exercise, %[a,b]	–2.6 (2.5)	–13 to 0		
Change in VAS with exercise, cm %[a,c]	2.4 (1.7)	0 to 6.1		
Change in FCS with exercise	0.49 (0.81)	–1 to 3		
QWB-SA score[d]	0.61 (0.12)	0.35 to 0.84		
Treatment at enrolment				
HS			2	4
rhDNase			39	83
Lung microbiology[e]				
Pseudomonas aeruginosa			22	48
Staphylococcus aureus			18	39
Stenotrophomonas maltophilia			1	2

[a] *42 children tested*
[b] *Change is calculated as the lowest percentage oxygen saturation during exercise minus the pre-exercise percentage oxygen saturation*
[c] *10-cm VAS with outcomes 'not at all short of breath' and 'the most breathless I have ever felt'. Change is calculated as post-exercise rating minus pre-exercise rating, positive changes indicating an increase in breathlessness*
[d] *Scores fall between the limits of 0 and 1 with higher scores indicating greater well-being*
[e] *Number of children with three positive sputum or cough swab cultures in the past year*

according to the protocol. HS made the patients cough during administration. Five patients complained of the salty taste of HS; however this was not severe enough for them to discontinue taking the treatment. There were ten patients (mean age 12.2 years, range 7.8 to 15.3 years) who were not already taking SABs. None of these patients developed a drop in FEV_1 of greater than 15% with the test dose of HS. The mean change in FEV_1 for these patients was –5% (range +10% to –13%).

Withdrawals from the study

In all, eight children were unable to complete the three treatment periods. *Figure 2* gives details of when these withdrawals occurred.

Four patients developed a severe decline in their pulmonary status, requiring a prolonged course of intravenous antibiotics, and these patients were withdrawn from the trial on clinical grounds. Two of them were taking alternate-day rhDNase, one was on HS and the other was on daily rhDNase. The baseline FEV_1 for these patients varied between 19 and 65% of predicted value, and so they were not all regarded as having the most severe lung disease.

Four children failed to complete two treatment periods and so were not included in the analyses comparing the treatments. One child completed two treatment periods, but did not complete the one in which daily rhDNase was to be received and so could not be included, as both treatment comparisons include daily rhDNase. In addition, three children were ineligible for HS due to bronchoconstriction following the test dose (discussed above). All three children had been randomly allocated to receive HS in the first treatment period and so their subsequent treatments were each brought forward one period as described in the protocol. Consequently 43 children were included in the analysis comparing daily with alternate-day rhDNase, and 40 children were included in the analysis comparing daily rhDNase with HS.

All children had their lung function tests carried out within the same 3-hour portion of the day and withheld SABs for at least 4 hours prior to the study visit.

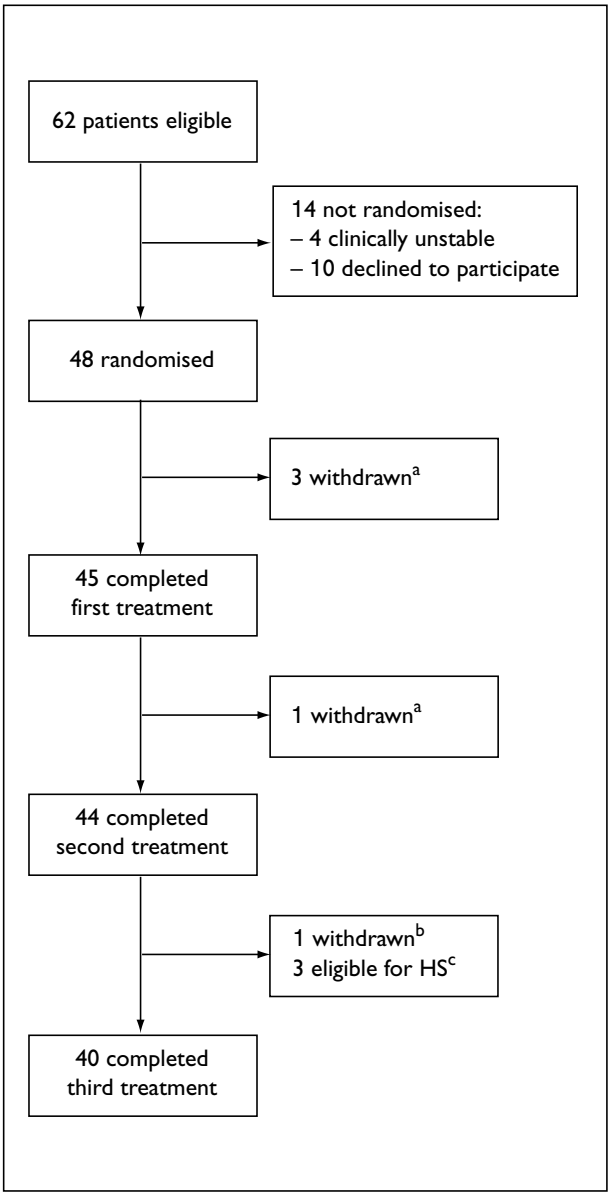

FIGURE 2 *Trial profile*

[a] *Withdrew due to severely deteriorating pulmonary status*
[b] *Underwent major liver surgery whilst taking HS*
[c] *Ineligible due to a fall in FEV_1 of greater than 15% with the first dose of HS, despite taking an SAB*

Clinical effectiveness

Primary outcome: FEV_1

Following 12 weeks of treatment, there was a mean increase in FEV_1 over baseline of 16% (SD 25%), 14% (SD 22%) and 3% (SD 21%) for daily rhDNase, alternate-day rhDNase and HS, respectively (*Table 2*). The most notable feature was the drop in FEV_1 over the treatment period for those children receiving HS in the third treatment period. Closer examination of the data revealed that this drop may have been recorded because there was a markedly high mean FEV_1 at the beginning of that treatment period; this could have masked a beneficial response to HS. The effectiveness of the washout period is discussed later in this chapter.

TABLE 2 *Mean percentage change in FEV_1 over baseline*

Treatment	Treatment period								
	One		Two		Three		All periods		
	n	Mean change (%)	*n*	Mean change (%)	*n*	Mean change (%)	*n*	Mean change (%)	SD (%)
Alternate-day rhDNase	16	14	17	18	10	9	43	14	22
Daily rhDNase	15	15	14	8	14	25	43	16	25
HS	12	8	12	12	16	–7	40	3	21
All treatments	43	12	43	13	40	8	126	11	23

Comparing the effects of the treatments in improving FEV_1 from baseline, daily rhDNase caused an 8% greater increase in FEV_1 compared with HS (95% CI, 2% to 14%; $p = 0.01$) (*Table 3*). However, there was no evidence of a difference for daily rhDNase compared with alternate-day rhDNase (2%; 95% CI, –4% to +9%; $p = 0.55$). Both treatments caused similar increases in FEV_1 over baseline. Statistical analyses ignoring the baseline measurements produced similar results.

The effect of the patient's disease severity on the relative treatment effects was assessed by dividing the study population into two groups: those with moderate lung disease and those with severe lung disease. The median FEV_1 at baseline for the study population was 49% of predicted value. The severe lung disease group contained those children whose mean baseline FEV_1 at the beginning of each treatment period was below the median (49%) for the whole group; the moderate lung disease group was the other half of the study population. No evidence was found of variation in the relative effects of treatments according to the severity of illness (*Table 3*). Therefore, regardless of baseline FEV_1, patients had a greater improvement in FEV_1 with daily rhDNase compared with HS and demonstrated no evidence of a difference in treatment effect between daily and alternate-day rhDNase.

There was variation in the individual responses to HS and rhDNase. *Figure 3* depicts the percentage change in FEV_1 with HS and daily rhDNase for individual children. Of the 40 children, 14 responded better with HS compared with daily rhDNase, and eight of these children had an improvement of 10% or more with HS. There were no defining features for these patients. One child (patient 'A') significantly deteriorated with both daily rhDNase and HS. Removing this patient from the analysis did not change the overall results.

Change in FVC

Following 12 weeks of treatment, there were statistically significant mean increases in FVC of 0.16 litres ($p = 0.003$) and 0.14 litres ($p < 0.001$) with daily rhDNase and alternate-day rhDNase, respectively (*Table 4*). However, HS caused a non-significant mean drop of 0.01 litres ($p = 0.85$). When the change in FVC with daily rhDNase was compared with those of alternate-day rhDNase (0.03 litres; 95% CI, –0.06 to 0.12; $p = 0.47$) and HS (0.08 litres; 95% CI, –0.03 to 0.18; $p = 0.16$), no significant differences were detected.

TABLE 3 *Percentage difference (with 95% CI) in FEV_1 between the treatments, adjusted for baseline*

	Daily rhDNase vs HS (*n* = 40)	Daily rhDNase vs alternate-day rhDNase (*n* = 43)
Percentage difference	+8% (2% to 14%)	+2% (–4% to 9%)
Percentage difference with adjustment[a]	+11% (5% to 17%)	+2% (–3% to 6%)
Subgroup analysis[a]		
Severe illness	+11% (3% to 20%)	+1% (–6% to 7%)
Moderate illness	+6% (–2% to 15%)	+3% (–3% to 10%)
p value[b]	0.29	0.63

[a] *Adjusted for treatment period, age at start of period, and season*
[b] p *value for difference between subgroups (test of interaction with severity of illness considered as a continuous variable*

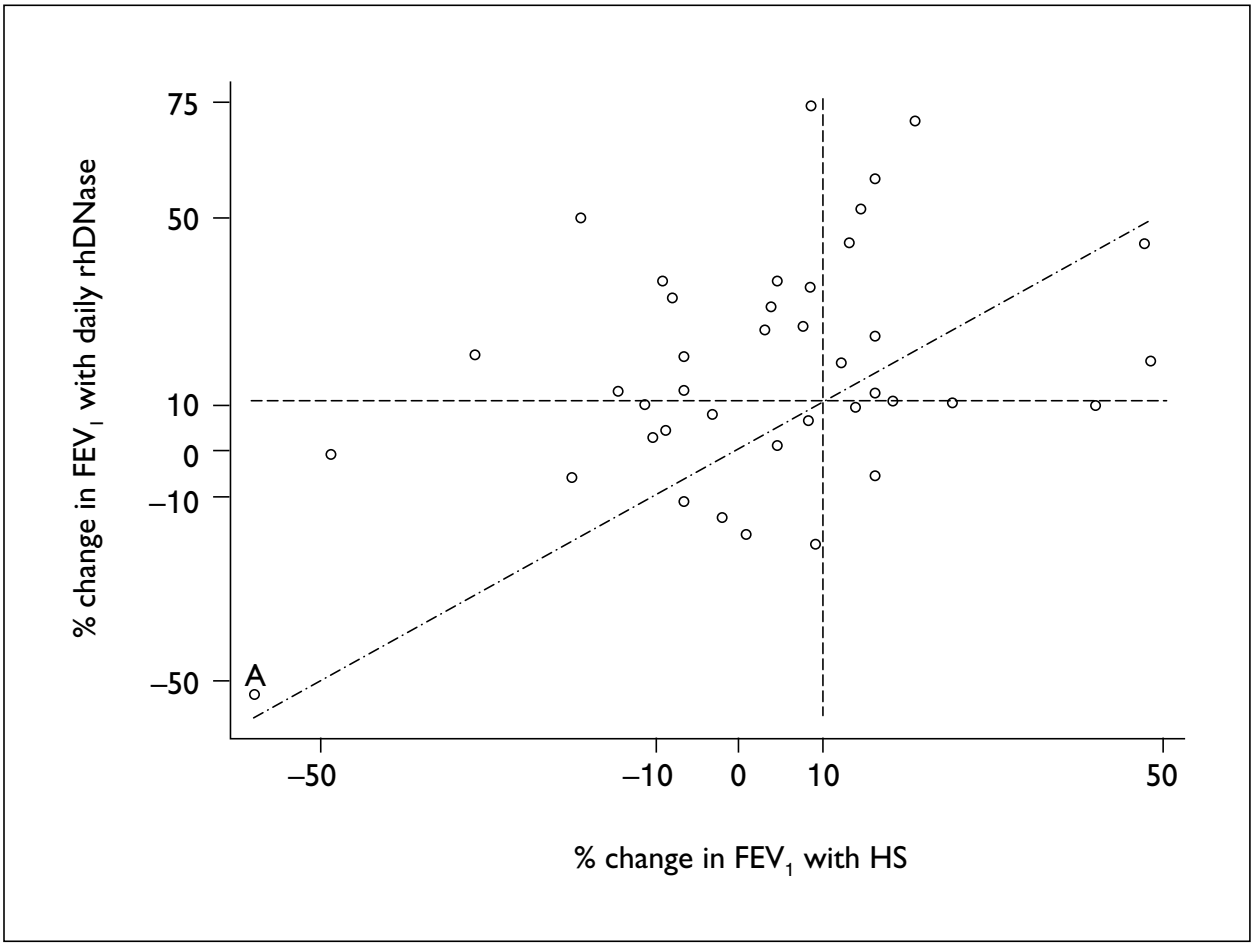

FIGURE 3 *Patients' responses to daily rhDNase and HS. Each point on the graph represents a patient*

TABLE 4 *Mean change in FVC in litres over each treatment period*

	Treatment period								
	One		Two		Three		All periods		
Treatment	*n*	Mean change	*n*	Mean change	*n*	Mean change	*n*	Mean change	SD
Daily rhDNase	15	0.08	14	0.06	14	0.35	43	0.16	0.34
Alternate-day rhDNase	16	0.17	17	0.14	10	0.10	43	0.14	0.20
HS	12	0.04	12	0.15	16	–0.18	40	–0.01	0.46
All treatments	43	0.10	43	0.12	40	0.07	126	0.10	0.35

Weight gain

In all three treatment periods, as anticipated, there was a mean increase in weight. There was a mean increase of 0.69 kg ($p = 0.03$) with daily rhDNase, 0.91 kg ($p = 0.001$) with alternate-day rhDNase, and 0.78 kg ($p = 0.002$) with HS (*Table 5*). There was a wide variation in the change in weight, with one child who had a gastrostomy tube inserted whilst taking alternate-day rhDNase increasing his weight from 34.5 kg to 44.8 kg during that treatment period. Excluding this child from the analysis did not alter the overall result. When the change in weight with daily rhDNase was compared with that with alternate-day rhDNase (–0.09 kg; 95% CI, –0.72 to 0.55; $p = 0.78$) and HS (–0.42kg; 95% CI, –1.03 to 0.20; $p = 0.18$), no significant differences were detected.

Exercise tolerance

At the beginning and end of each treatment period, patients performed the 3-minute step test.

TABLE 5 *Mean change in weight in kg over each treatment period*

Treatment	Treatment period								
	One		Two		Three		All periods		
	n	Mean change	*n*	Mean change	*n*	Mean change	*n*	Mean change	SD
Daily rhDNase	15	0.99	14	1.04	14	0.02	43	0.69	2.04
Alternate-day rhDNase	16	1.65	17	0.44	10	0.53	43	0.91	1.69
HS	12	1.30	12	0.21	16	0.83	40	0.78	1.53
All treatments	43	1.32	43	0.57	40	0.47	126	0.80	1.76

As part of the step test, the changes in SaO_2, the VAS and the FCS were recorded.

Oxygen saturation

For this outcome the raw measure is the drop in percentage SaO_2 during exercise, that is, the minimum SaO_2 minus the pre-exercise SaO_2. Hence a large negative value indicates a large drop in SaO_2 with exercise, and therefore an adverse response.

The values given in *Table 6* are the mean differences between the post-treatment drop in SaO_2 and the pretreatment drop in SaO_2. Hence a positive value indicates less of a drop in SaO_2 with exercise, following treatment, or in other words, a beneficial effect of treatment on exercise tolerance.

Comparing treatments, in the following estimated effects a positive value indicates that SaO_2 is better maintained with daily rhDNase (i.e. there is improved exercise tolerance). Daily rhDNase versus HS gave a value of –0.06% (95% CI, –0.94 to 0.83; $p = 0.90$), and daily rhDNase versus alternate-day rhDNase gave a value of 0.18% (95% CI, –0.73 to 1.09; $p = 0.69$); no evidence of treatment differences was demonstrated.

VAS for breathlessness

For this outcome the raw measure is the difference in VAS following exercise, that is, the post-exercise VAS minus the pre-exercise VAS. A large VAS indicates greater breathlessness, hence a positive difference indicates an increase in breathlessness after exercise. The values given in *Table 7* are mean differences between the post-treatment change in VAS and the pretreatment change in VAS. Hence a positive value indicates a greater increase in breathlessness with exercise (i.e. decreased exercise tolerance) following treatment.

Comparing treatments, in the following estimated effects, a positive value indicates breathlessness increases more with daily rhDNase. Daily rhDNase versus HS gave a value of 0.38 (95% CI, –0.15 to 0.92; $p = 0.16$), and daily rhDNase versus alternate-day rhDNase gave a value of 0.10, (95% CI, –0.37 to 0.57; $p = 0.67$); no evidence of treatment differences was demonstrated.

FCS

For this outcome the raw measure is the increased number of breaths required to count to 15 following exercise, that is the post-exercise number of breaths minus the pre-exercise number of breaths needed to count to 15.

TABLE 6 *Effect of each treatment on the drop in oxygen saturation with the 3-minute step test. A positive value indicates less of a drop in oxygen saturation with exercise, following treatment, that is, a beneficial effect of treatment on exercise tolerance*

Treatment	Treatment period								
	One		Two		Three		All periods		
	n	Mean change	*n*	Mean change	*n*	Mean change	*n*	Mean change	SD
Daily rhDNase	15	0.46	14	–0.50	14	1.00	43	0.28	2.38
Alternate-day rhDNase	16	0.29	17	–0.79	10	0.40	43	–0.08	1.85
HS	12	0.73	12	–0.11	16	0.12	40	0.25	2.22
All treatments	43	0.47	43	–0.51	40	0.47	126	0.15	2.15

TABLE 7 *Effect of each treatment on the change in the VAS with the 3-minute step test. A positive value indicates a greater increase in breathlessness with exercise (i.e. decreased exercise tolerance) following treatment*

	Treatment period								
	One		Two		Three		All periods		
Treatment	*n*	Mean change	*n*	Mean change	*n*	Mean change	*n*	Mean change	SD
Daily rhDNase	15	–0.69	14	0.74	14	0.26	43	0.11	1.83
Alternate-day rhDNase	16	0.24	17	0.22	10	0.47	43	0.29	1.50
HS	12	–0.55	12	0.06	16	–0.23	40	–0.26	1.53
All treatments	43	–0.31	43	0.38	40	0.11	126	–0.06	1.63

The values given in *Table 8* are mean differences between the post-treatment increase in breaths and the pretreatment increase in breaths. Hence a positive value indicates a greater increase in breathlessness with exercise (i.e. reduced exercise tolerance) following treatment.

Comparing treatments, in the following estimated effects a positive value indicates breathlessness increases more with daily rhDNase. Daily rhDNase versus HS gave a value of –0.05 breaths (95% CI, –0.44 to 0.34; $p = 0.79$), and daily rhDNase versus alternate-day rhDNase gave a value of 0.00 breaths, 95% CI, –0.44 to 0.44; $p = 1.00$); no evidence of treatment differences was demonstrated.

QoL score

Following 12 weeks of treatment, there was a non-significant change from baseline in mean QWB score of 0.03 with daily rhDNase ($p = 0.17$), of 0.03 with alternate-day rhDNase, and 0 with HS ($p = 0.81$) (*Table 9*). When the change in QWB score with daily rhDNase was compared with that for alternate-day rhDNase (0.01; 95% CI, –0.02 to 0.04; $p = 0.58$) and HS (0.03; 95% CI, –0.02 to 0.07; $p = 0.22$), no evidence of treatment differences was detected.

TABLE 8 *Effect of each treatment on the change in the FCS with the 3-minute step test. A positive value indicates a greater increase in breathlessness with exercise (i.e. reduced exercise tolerance) following treatment*

	Treatment period								
	One		Two		Three		All periods		
Treatment	*n*	Mean change	*n*	Mean change	*n*	Mean change	*n*	Mean change	SD
Daily rhDNase	15	–0.31	14	0.71	14	0.08	43	0.18	1.25
Alternate-day rhDNase	16	0.14	17	0.14	10	0.20	43	0.16	0.79
HS	12	0.50	12	0.00	16	–0.19	40	0.06	0.84
All treatments	43	0.081	43	0.32	40	0.00	126	0.13	0.98

TABLE 9 *Mean change in QWB score over each treatment period*

	Treatment period								
	One		Two		Three		All periods		
Treatment	*n*	Mean change	*n*	Mean change	*n*	Mean change	*n*	Mean change	SD
Daily rhDNase	15	0.06	14	0.03	14	–0.01	43	0.03	0.13
Alternate-day rhDNase	16	0.06	17	0.01	10	0.01	43	0.03	0.12
HS	12	–0.01	12	0.05	16	–0.04	40	0.00	0.10
All treatments	43	0.04	43	0.03	40	–0.02	123	0.02	0.12

Pulmonary exacerbations

For each trial drug, the numbers of treatment periods where an individual had one or more pulmonary exacerbations were compared. During the HS, daily rhDNase and alternate-day rhDNase treatment periods 15, 18, and 17 children, respectively, experienced one or more pulmonary exacerbations,. There was no evidence of differences between treatments, as the exact McNemar significance probability was 1.00 when daily rhDNase was compared with alternate-day rhDNase and HS.

Results of the economic evaluation

The mean total length of hospital stay, in particular that resulting from pulmonary exacerbations, was higher during the HS compared with the daily rhDNase treatment periods, and also during alternate-day compared with daily rhDNase treatment periods (*Table 10*). However, the CIs for these differences spanned zero.

The drug cost per day was £0.38 for HS, £20.39 for daily rhDNase and £10.20 for alternate-day rhDNase. The average total cost of an occupied bed-day ranged from £280 to £397, that of an outpatient consultation from £51 to £84, and that of a ward review from £67 to £148 (*Table 11*). The unit costs were generally higher in the two postgraduate hospitals compared with the DGHs, mainly because of the higher costs of overheads and capital.

Over the 12-week treatment period the mean drug cost of daily rhDNase was £1755 compared with £37 for HS. The difference between the intervention costs was not offset by lower hospital and community care costs. Over 12 weeks the mean total health service cost for the daily rhDNase treatment period was £5694 compared with £4285 for HS, a mean difference of £1409 (95% CI, £440 to £2318) (*Table 12*). In the daily rhDNase and alternate-day rhDNase comparison, the lower hospital costs during daily rhDNase did not offset the increased intervention costs. The mean total cost during daily rhDNase was £5711 compared with £5198 during the alternate-day period, a mean difference of £513 (95% CI, –£546 to £1510) (*Table 12*). While the intervention costs were on average a higher proportion of total costs during the rhDNase periods, the costs of other resources, in particular antibiotic therapies, were also important components of total costs (*Figure 4*).

Sensitivity analyses were carried out on the price of rhDNase, because in practice the actual price providers pay is likely to be lower than the *British National Formulary*[39] price, and on the cost per hospital day, as this may vary according to the setting considered. The analysis used the values from the 20th and 80th percentiles of the costs per occupied bed-day from a UK national database.[169] The results showed that after reducing the rhDNase costs by 10% and 30%, the mean additional costs of rhDNase compared with HS fell to £1234 (95% CI, £264 to £2204), and £884 (95% CI, –£86 to £1855), and the mean additional costs of daily compared with alternate-day rhDNase

TABLE 10 *Comparison between the treatments for mean healthcare use*

	Daily rhDNase vs HS			Daily rhDNase vs alternate-day rhDNase		
	Daily rhDNase (*n* = 40)	HS (*n* = 40)	Mean difference (95% CI)	Daily (*n* = 43)	Alternate (*n* = 43)	Mean difference (95% CI)
Hospital resource use						
Hospital admissions	0.63	0.53	0.10 (–0.15 to 0.35)	0.63	0.79	–0.16 (–0.41 to 0.09)
Inpatient days						
Total	4.73	5.13	–0.40 (–2.32 to 1.52)	4.47	5.40	–0.93 (–3.24 to 1.38)
Due to pulmonary exacerbation	2.33	4.28	–1.95 (–4.22 to 0.32)	2.21	2.91	–0.70 (–2.74 to 1.34)
Outpatient visits	0.93	1.23	–0.30 (–0.71 to 0.11)	1.00	0.86	0.14 (–0.28 to 0.56)
Day-case visits	0.33	0.35	–0.03 (–0.30 to 0.25)	0.37	0.40	–0.02 (–0.31 to 0.27)
Days of intravenous antibiotic therapy	9.45	10.38	–0.93 (–4.45 to 2.60)	9.56	8.84	0.72 (–2.36 to 3.81)
Community service use						
GP contacts	0.30	0.25	0.05 (–0.17 to 0.27)	0.28	0.21	0.07 (–0.14 to 0.28)
Nurse contacts	1.75	2.70	–0.95 (–0.17 to 0.25)	1.70	2.26	–0.56 (–3.43 to 2.32)
Physiotherapist contacts	0.33	0.10	0.23 (–0.09 to 0.54)	0.30	0.12	0.19 (–0.02 to 0.39)

TABLE 11 *Average unit costs (£) of hospital care for each of the study centres*

	Postgraduate centre 1	Postgraduate centre 2	DGH
Inpatient care (per occupied bed-day)			
Doctors' time	34.42	54.21	31.53
Nurses' time	116.92	80.17	111.94
Other healthcare staff time	45.47	22.46	22.31
Consumables	15.98	17.56	20.00
Overheads	116.74	168.23	55.79
Capital costs	52.69	54.70	38.65
Total	**382.03**	**397.33**	**280.22**
Outpatient clinic (per consultation)			
Doctors' time	13.33	12.58	11.92
Nurses' time	3.57	2.24	3.00
Other healthcare staff time	4.91	5.54	0
Consumables	3.99	4.39	10.00
Overheads	29.18	42.06	13.95
Capital costs	16.86	17.50	12.37
Total	**71.85**	**84.31**	**51.24**
Ward review (per consultation)			
Doctors' time	13.33	12.58	2.00
Nurses' time	21.40	13.46	7.95
Other healthcare staff time	0	1.99	0
Consumables	7.99	8.78	10.00
Overheads	58.37	84.11	27.89
Capital costs	26.35	27.35	19.33
Total	**127.43**	**148.28**	**67.17**

were £425 (95% CI, –£594 to £1443) and £246 (95% CI, –£771 to £1262). The results were insensitive to changes in the cost per bed-day: for example varying the cost per bed-day from £187 to £120 meant that the incremental costs of daily rhDNase compared with HS ranged from £1548 (95% CI, £982 to £2114) to £1521 (95% CI, £845 to £2198).

The cost analysis assumed that the utilisation of each of the treatments was that prescribed by the study protocol. However, it was found in the study that patients did not return either a diary or the treatment containers for daily rhDNase in six cases, for HS in three cases, and for alternate-day rhDNase in three cases. Following the daily rhDNase treatment period, 33 children returned diaries which indicated a mean of 96% adherence with prescribed doses and 32 children returned treatment packs which indicated 84% adherence. Following the HS treatment period, 32 children returned diaries which indicated a mean of 93% adherence with prescribed doses, and 32 children returned treatment packs which also indicated a mean of 93% adherence. Finally, following the alternate-day rhDNase period 39 children returned diaries which indicated 98% adherence with the prescribed doses, and 36 children returned treatment packs which indicated 84% adherence.

Rather than assuming that the patients' drug utilisation was as specified by the protocol, it would have been possible to use the data on adherence to adjust the cost estimates. However, the adherence results suggested that adherence rates were high and similar across the treatment regimens. This suggests that assuming the patients were adherent to the medications concerned would have had little effect on the relative costs of the interventions. One problem with adjusting the cost estimates is that although patients may have not returned all the treatment packs, this may be because they had lost or disposed of the packs, which would therefore still have led to the same cost to the NHS.

Cost-effectiveness analysis

In the comparison of cost-effectiveness analysis, the comparisons were conducted across all

TABLE 12 *Mean costs (£) and proportions of total costs (%) over each 12-week treatment period*

	Daily rhDNase vs HS				Daily rhDNase vs alternate-day rhDNase			
	Daily rhDNase (*n* = 40)		HS (*n* = 40)		Daily (*n* = 43)		Alternate (*n* = 43)	
	Mean (£)	%	Mean (£)	%	Mean (£)	%	Mean (£)	%
Intervention	1755	30.8	37	0.9	1749	30.6	857	16.5
Non-intervention drugs								
I.v. antibiotics	601	10.6	748	17.5	679	11.9	702	13.5
Oral antibiotics	95	1.7	112	2.6	101	1.8	110	2.1
Other drugs	1575	27.7	1503	35.1	1587	27.8	1537	29.6
Subtotal	2271	39.9	2364	55.2	2367	41.4	2349	45.2
Hospital care								
Inpatient	1483	26.0	1669	39.0	1404	24.6	1769	34.0
Outpatient	49	0.9	48	1.1	60	1.0	53	1.0
Ward review	56	1.0	89	2.1	50	0.9	46	0.9
Investigations	26	0.5	29	0.7	28	0.5	50	1.0
Procedures	30	0.5	18	0.4	29	0.5	49	0.9
Subtotal	1643	28.9	1855	43.2	1571	27.5	1968	37.9
Community care								
GP contacts	7	0.1	18	0.1	7	0.1	5	0.1
Other contacts	18	0.3	22	0.5	17	0.3	19	0.4
Subtotal	25	0.4	28	0.7	24	0.4	24	0.5
Grand total	**5694**		**4285**		**5711**		**5198**	
Mean difference (95% CI)	**1409 (440 to 2318)**				**513 (–546 to 1510)**			

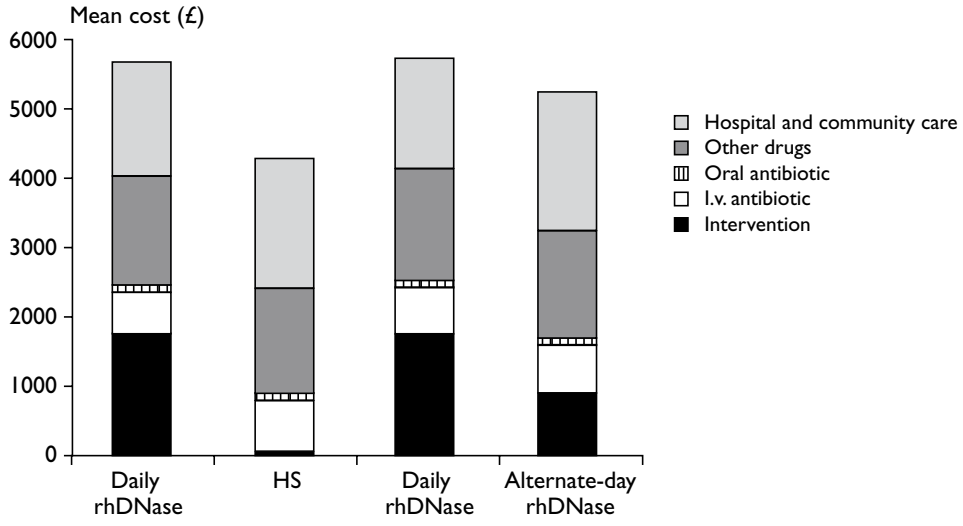

FIGURE 4 *Mean total cost of daily rhDNase compared with HS, and daily rhDNase compared with alternate-day rhDNase*

three treatment groups and, as detailed in the statistical section, the primary outcome data were compared across the treatment groups using a method which was more amenable for use in cost-effectiveness calculations than that used for the main trial analysis. The implications of using this form of analysis for the key parameters in the cost-effectiveness investigation are illustrated by *Table 13*. Of particular interest is that the mean improvement in FEV_1 after 12 weeks of HS was estimated at 0% compared with 3% in the principal trial analysis. This reflected the exclusion of three cases from the analysis, and the use of a different method of analysis.

The bootstrap samples plotted on the cost-effectiveness plane (*Figure 5*) show the uncertainty surrounding the mean estimate of cost-effectiveness reported by the ICER. The problem of interpreting negative ratios is illustrated in *Figure 5(b)*, where bootstrap samples fall in all four quadrants. Therefore an ICER of –£200 per 1% gain in FEV_1 might represent improved outcomes and lower costs for daily compared with alternate-day rhDNase, or worse outcomes and higher costs. This means that a meaningful ordering of the ratios, which is required to make CIs around the ICER interpretable, is impossible.

Figure 6 shows the CEAC for each of the three comparisons. If the decision maker had an R_c of £200 per 1% gain in FEV_1 the probability of daily and alternate-day rhDNase proving cost-effective, compared with HS, would be 0.91 and 0.88. For the same R_c the probability of daily rhDNase being cost-effective, compared with alternate-day rhDNase, is 0.49.

The mean ICER for each comparison corresponded closely to the R_c when the probability of one intervention being cost-effective was 0.5. The CEAC cuts the vertical axis at the one-sided p value for the cost difference (0.001 for daily rhDNase versus HS), and asymptotes to 1 minus the one-sided p value of the effectiveness difference (0.999 for daily rhDNase versus HS).

Assuming that R_c = £200 per 1% increase in FEV_1, then the mean net benefits of daily and alternate-day rhDNase compared with HS were £1158 (95% CI, –621 to 2842) and £1188 (95% CI, –847 to 3343), respectively (*Table 13*). At this R_c, the net benefit of daily compared to alternate-day rhDNase was –£30 (95% CI, –2091 to 1576).

The sensitivity analysis did not find the results to be sensitive to the unit costs of hospital services, but changing the price of rhDNase was somewhat more important. For example, the probability of daily rhDNase being cost-effective compared with alternate-day rhDNase, when R_c = £200 per 1% gain in FEV_1, rose from 49% to 59% corresponding to a reduction in price of rhDNase of 0% to 30% (*Figure 7*).

Effectiveness of the washout period

The length of the washout period varied from 2 to 4 weeks. It was important to assess the effectiveness of the washout period as changes from baseline were assessed for many of the outcomes. A complete washout of the previous treatment prior to commencement of the next treatment period was needed, with no carry-over effect. In addition, any decline below baseline in lung function during the washout period had to be monitored. The effects of the washout period were assessed by analysing the mean baseline FEV_1 values for each of the three trial drugs depending on the treatment period of administration (*Table 14*).

TABLE 13 *Mean incremental cost, incremental effectiveness and net benefit over 12 weeks (with 95% CIs)*

	Daily rhDNase–HS	Daily rhDNase–alternate-day rhDNase	Alternate-day rhDNase–HS
Total cost, £	1409 (354 to 2277)	464 (–647 to 1510)	945 (–509 to 2301)
Effectiveness, % FEV_1	14 (5 to 23)	2 (–6 to 12)	12 (2 to 22)
ICER, £ per 1% gain in FEV_1	110	214	89
Mean net benefit, £			
R_c = £400 per 1% gain in FEV_1	3725 (585 to 6701)	403 (–3303 to 3341)	3321 (–116 to 6976)
R_c = £200 per 1% gain in FEV_1	1158 (–621 to 2842)	–30 (–2091 to 1576)	1188 (–847 to 3343)
R_c = £100 per 1% gain in FEV_1	–126 (–1293 to 1041)	–246 (–1596 to 909)	121 (–1323 to 1752)

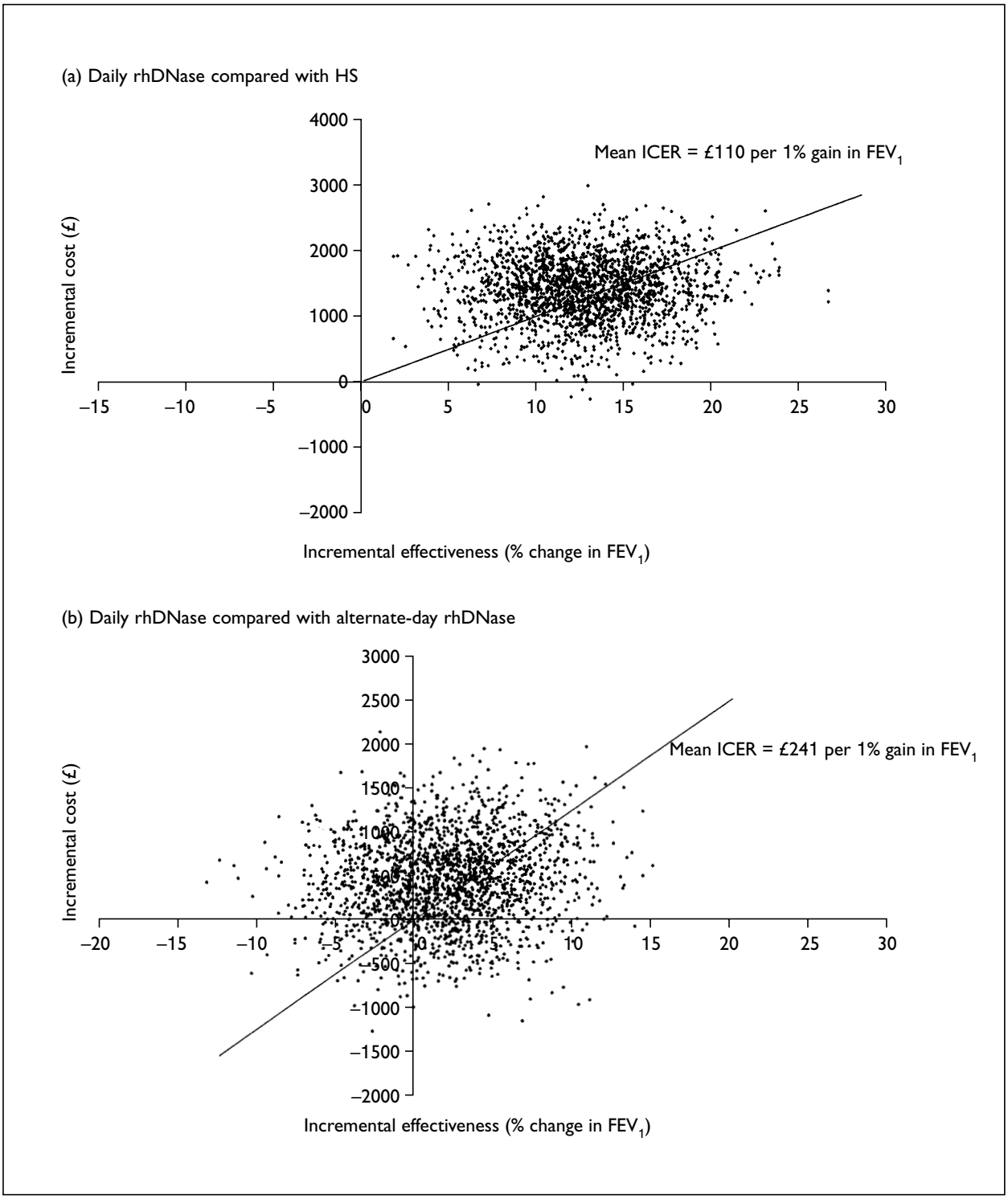

FIGURE 5 *Results on the cost-effectiveness plane. (a) Daily rhDNase compared with HS. (b) Daily rhDNase compared with alternate-day rhDNase*

For the study group, the mean baselines at the beginning of treatment periods 1 and 2 (final row of *Table 14*) were similar, suggesting a return to baseline of FEV_1 following the washout period. However, the baseline FEV_1 of treatment period 3 is unusually high, mainly due to the high baseline FEV_1 for patients commencing HS in this period. This may also possibly contribute to the apparently poor performance of HS in this period. This high value could be due to any one or more of a number of factors: chance occurrence, selective drop-out, or carry-over.

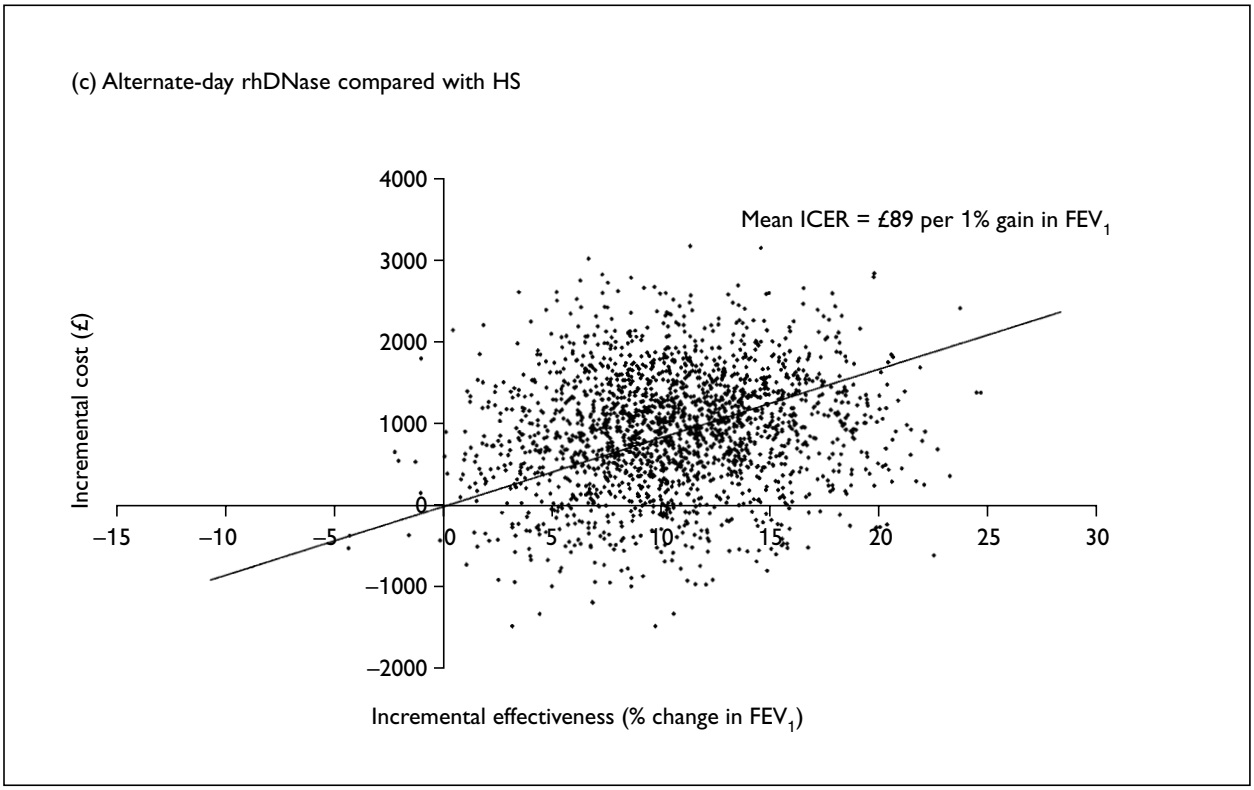

***FIGURE 5* contd** *Results on the cost-effectiveness plane. (c) Alternate-day rhDNase compared with HS*

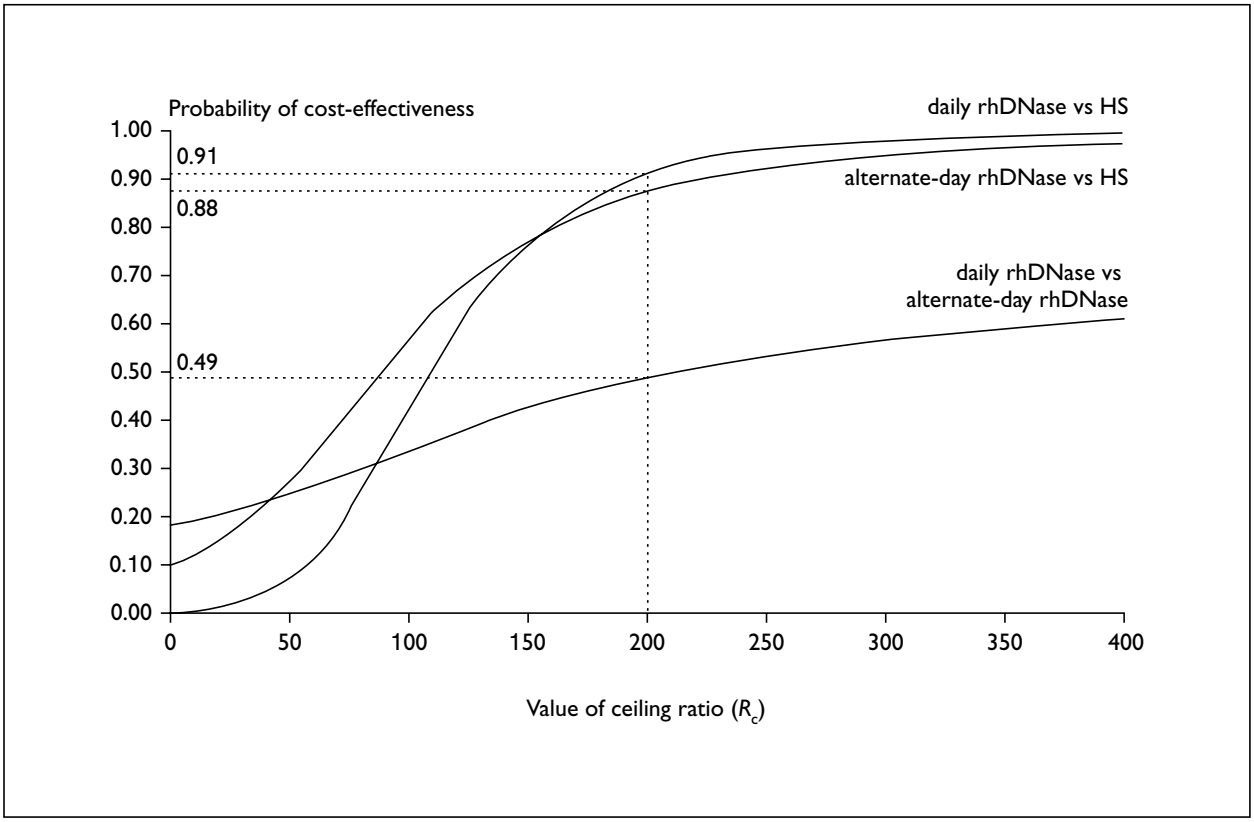

FIGURE 6 *Cost-effectiveness acceptability curves*

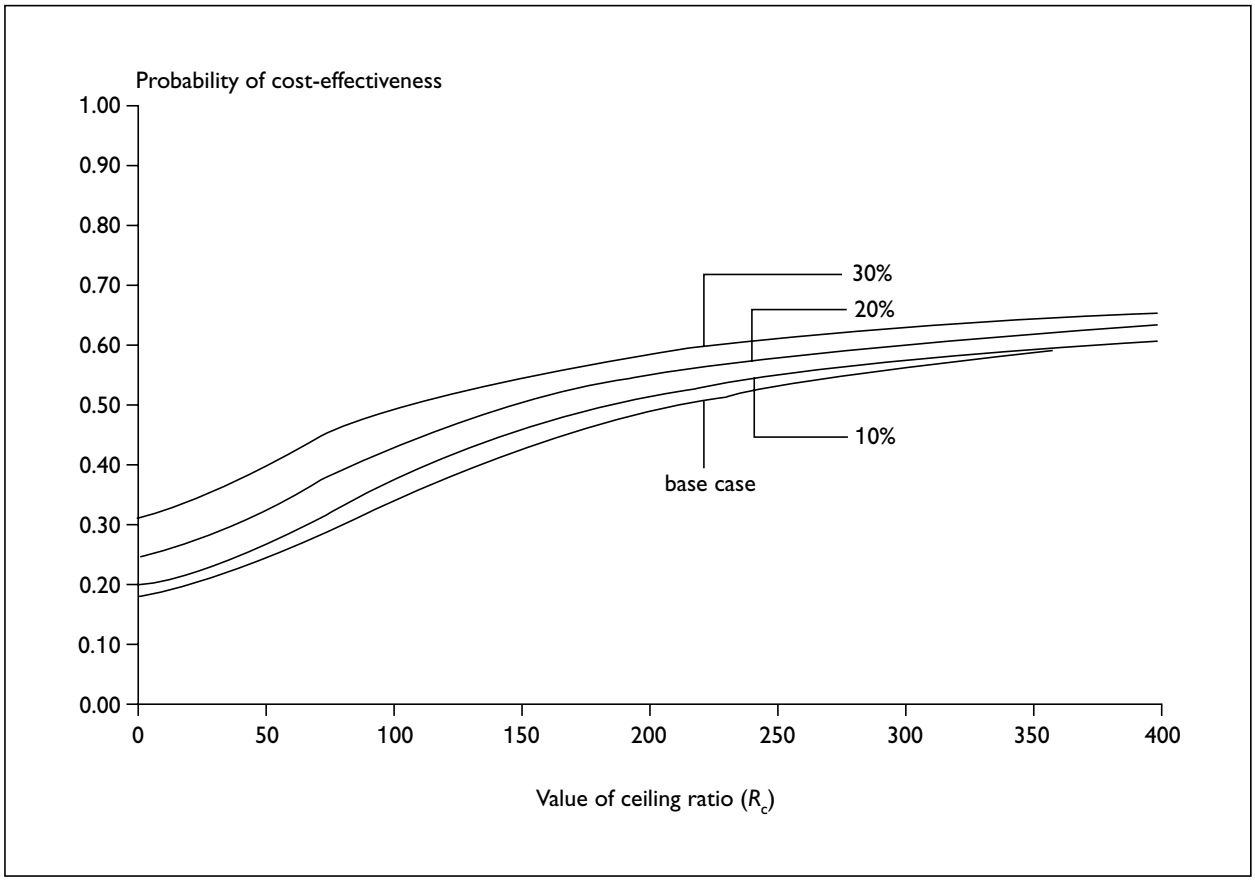

FIGURE 7 *Sensitivity analysis: the effect of changes in the price of rhDNase on the CEAC of daily versus alternate-day rhDNase*

TABLE 14 *Mean baseline FEV_1, in litres, at the beginning of each treatment period*

	Treatment period							
	One		Two		Three		All periods	
Treatment to be commenced	***n***	**Mean**	***n***	**Mean**	***n***	**Mean**	***n***	**Mean**
Daily rhDNase	17	1.04	14	1.29	14	1.22	45	1.17
Alternate-day rhDNase	16	1.25	17	1.14	10	1.22	43	1.20
HS	12	1.31	12	1.17	16	1.48	40	1.34
All treatments	45	1.18	43	1.20	40	1.33	128	1.23

Two patients who were randomly allocated to have HS as their third treatment required intravenous antibiotics during the washout period. Their baseline FEV_1 was high for the HS period which might have been caused by the antibiotics, thus increasing the mean baseline for all of the group who had HS as their third treatment. Omitting these two patients, however, did not affect the overall comparison of daily rhDNase and HS.

Adverse events

There was no evidence of any differences between treatments with regard to the number of adverse events (*Table 15*). Lung microbiological examination was done for the children who completed the HS treatment period. None of these children had developed a new isolation of *Pseudomonas aeruginosa* or had an increase in staphylococcal infection.

TABLE 15 *Number of patients having adverse events during the study. The ten most frequent adverse events have been listed*

Adverse event	HS (*n* = 40)	Daily rhDNase (*n* = 43)	Alternate-day rhDNase (*n* = 43)
Increased cough	13	17	23
Coryza	5	3	3
Throat infection	6	2	2
Allergic reaction to antibiotic	1	0	2
Wheeze	1	2	1
Breathlessness	2	1	4
Haemoptysis	0	0	2
Chest pain	1	0	0
Eye irritation	1	1	0
Oral thrush	1	1	0

Chapter 4
Discussion

Interpretation of the results

This study has shown that, over 12 weeks, daily rhDNase causes a significantly greater increase in FEV_1 than HS. Comparing daily rhDNase with alternate-day rhDNase, both treatments caused similar increases in FEV_1. None of the secondary outcomes showed a significant difference between the treatments. The mean difference in cost for 12 weeks' treatment was £1409 between daily rhDNase and HS, and £513 between daily and alternate-day rhDNase. If decision makers are prepared to pay £200 for a 1% increase in FEV_1 over a 12-week period, the probability of daily or alternate-day rhDNase proving cost-effective compared with HS is substantially greater than 50%. At this R_c, the mean net benefits of daily rhDNase compared with HS are positive, but with wide CIs, illustrating the uncertainty which surrounds these results.

Tolerability of HS

When administered using our protocol, 7% HS was well tolerated. Despite its having to be given twice a day, adherence to HS treatment was similar to that for daily and alternate-day rhDNase. Furthermore, there was no increased risk of *P. aeruginosa* isolation or pulmonary exacerbation with HS compared with rhDNase. However, the study duration may not have been long enough for any significant difference to become apparent.

With the test dose of HS only two children had a drop in FEV_1 of greater than 15%. One child refused to continue with the test dose of HS as it made her breathless. She refused to perform spirometry after the HS dose, so we were unable to measure the change in FEV_1. The study used a drop in FEV_1 of greater than 15% as the measure of severe bronchoconstriction. Other studies have used a 20% drop as a measure; however we believed that to ensure safety a slightly lower decline in FEV_1 should be used. In the two patients who displayed severe bronchoconstriction, their FEV_1 measurements actually dropped by more than 20%.

It would have been ideal to have withdrawn SAB from all patients prior to administering the dose of HS, as this would have given us the true effect of HS on the airways. However this would not have been practical or ethical. Rodwell and Anderson[67] had shown that the majority of CF patients responded to inhaled 10% HS with progressive and sustained airway narrowing, as observed in asthma, or by transient airway narrowing. Patients who were on SABs in our study were taking them on the basis of bronchial response testing with SABs within the last year. Therefore they had bronchial hyper-reactivity and administering HS without premedication with SABs would have been unsafe.

Most of the patients on SABs were taking them prior to CPT twice a day. HS was also to be administered twice daily prior to CPT, therefore the patients would be taking the SAB prior to HS, once HS treatment was commenced. The purpose of giving the test dose of HS was to see whether they would tolerate HS as part of daily therapy, rather than to assess hyper-responsiveness as a provocation test.

In two previously published short-term studies of HS, patients have been given a test dose of HS prior to commencing therapy.[62,63] In both studies all patients had premedication with salbutamol and HS was shown to be well tolerated. Eng and colleagues[63] gave 600 µg of salbutamol from a metered-dose inhaler via a Volumatic, followed by 6% HS, in 58 patients. The FEV_1 was measured before the bronchodilator was given and after HS administration. Only one patient had a drop in FEV_1 of greater than 15%. Riedler and colleagues[62] used 5 mg of nebulised salbutamol and 7% HS in ten patients. No patient had a drop in FEV_1 of greater than 10% following HS.

In our study, none of the patients who were not on an SAB had a significant drop in FEV_1 with HS, and therefore none of them required SABs. We did not give SABs to those patients not already taking them, as in some patients SABs have been shown to cause bronchoconstriction. Furthermore, we did not want to introduce another medication into the patients' treatment regime if it was not going to be of benefit to them.

Overall evidence for the results

Previous studies have shown that HS improves mucociliary clearance and sputum expectoration in patients with CF.[60–62] However, there have been only two randomised trials which have assessed lung function changes with continuous use of HS, both of which were short-term. Eng and colleagues[63] compared 2 weeks' treatment with 6% HS or IS in a parallel trial. They found a significant improvement in mean FEV_1 of 15% for HS compared with 2.8% for IS. In the second study, which has been presented in abstract form only, Ballmann and von der Hardt[64] performed a small pilot crossover trial comparing daily rhDNase with 5.85% HS. A total of 14 CF patients received 3 weeks of each treatment in random order, with a 3-week washout period between treatments. Increases in mean FEV_1 were 7.7% and 9% for HS and rhDNase, respectively. However, statistical testing was not performed because of the small numbers involved.

Both these short-term studies showed greater improvements in mean FEV_1 with HS than were found in our study. However, the initial increase in FEV_1 caused by HS after the first few weeks of therapy may not be sustained in the medium or long term by all patients. This has also been shown to occur with rhDNase. Fuchs and colleagues[15] found that the initial improvement in FEV_1 of approximately 9% with rhDNase declined over the first month and remained stable at between 5% and 6% thereafter.

In both the previous studies a larger volume (10 ml) of HS was administered. However, the time taken to deliver a nebulised drug is important for patient adherence.[90] Ultrasonic nebulisers tend to deliver a larger volume over a shorter period of time, but are not recommended for rhDNase[20] and are generally not used for domiciliary therapy in CF. Ballmann and von der Hardt[64] reported that it took about 84 minutes to administer 10 ml of HS delivered twice a day by jet nebuliser. This long inhalation time was unacceptable to the patients and the authors suggested that if this regime was instituted as permanent therapy, there would be problems with adherence. Our trial had to be pragmatic, and a volume of 5 ml of 7% HS, which takes about 10 minutes to administer by jet nebuliser, was used.

There was also a marked variation in individual response to the treatments, which has also been found in previous studies of rhDNase.[15,24] About 50% of the patients on daily rhDNase and about 35% on HS had an improvement in FEV_1 of over 10%. Previous attempts at predicting the response to rhDNase for an individual patient on the basis of pretreatment clinical data have failed.[24] Therefore to assess response to rhDNase, most CF centres have developed formal *n*-of-1 trials of treatment to find out who benefits and to justify prescribing the agent. As one-third of patients respond significantly with HS, patients not responding to rhDNase may show a beneficial response with HS.

The evidence from the cost-effectiveness analyses was that either rhDNase strategy may be regarded as cost-effective if decision makers are prepared to pay at least £200 over a 12-week period for a 1% gain in FEV_1 (or £2000 for a 10% gain in FEV_1). Compared with daily rhDNase the costs of alternate-day rhDNase were £500 lower over 12 weeks, although this difference was not statistically significant.

An important aspect of our study was that, in keeping with the general guidelines on economic evaluation, it took a broad perspective of resource-use measurement. This meant that it was possible to assess whether the costs of rhDNase were offset by savings in hospital and community health services, or in the use of other drugs. Oster and colleagues,[40] in a previous economic evaluation of rhDNase, hypothesised that health service cost savings would offset one-third of the drug's cost. Our study did not provide any strong evidence that daily rhDNase reduced the rate of inpatient admissions or the duration of use of intravenous antibiotics. However it suggested that the length of stay for pulmonary exacerbations (the primary reason for admission) was on average 1.95 days longer following HS rather than daily rhDNase treatment, although the CIs around the estimate were wide.

A key determinant of the incremental costs of the rhDNase strategies was the cost of the drug itself. In the base case analysis the unit cost of the drug was taken from the *British National Formulary*,[39] which is recommended practice for reporting results in a generalisable way. However, if providers can negotiate a lower price for rhDNase, the incremental cost falls proportionately. By contrast, the sensitivity analysis showed that the results were reasonably robust to the particular cost per day used for a hospital provider.

This study did not take a societal perspective and measure the relative costs to the patient and the family. The finding that community service use, in

particular, was very similar between the groups, suggests that taking a broader outlook would have been unlikely to change the results. Resource use directly attributable to the administration of the trial was excluded from the analysis. The only outstanding 'trial effect' may be that in the trial, patients substituted attendance at postgraduate hospital clinics for DGH clinic visits. This effect is unlikely to vary between the treatment arms, so the impact on the incremental costs of the rhDNase therapy is likely to be negligible. However, the length of follow-up was only 12 weeks, so that any improvements in lung function from the rhDNase therapy which led to reductions in resource use after this period, were not included. Nevertheless, in the study by Oster and colleagues[40] the maximum difference in the cumulative incidence of RTI (the main reason for hospital admission), occurred after 4 weeks of therapy.

The detailed approach to costing meant that resource use and total cost were measured for each patient, so it was possible to report mean effect sizes with 95% CIs for the parameters of interest. The difference between the total cost of alternate-day and daily rhDNase of £513 over 12 weeks, which might be regarded as important from a decision maker's viewpoint, was not found to be statistically significant. For the observed difference in costs to have been statistically significant would have required about four times as many patients. This illustrates a general concern about economic evaluations in parallel with randomised controlled trials, namely that the sample size may be too small to reliably detect differences in economic end-points. This problem usually arises because the sample size is calculated, as in this study, to detect a clinically significant difference in the primary efficacy outcome measure.

This study provided, for the first time, detailed estimates of the relative costs and cost-effectiveness of different treatment strategies for CF. The results show that while rhDNase improves outcomes, this is at an increased cost. In such circumstances a full cost-effectiveness analysis was able to summarise the results using a single measure of cost-effectiveness, in this case the additional cost per 1% gain in FEV_1.

As this is the first study to present a full cost-effectiveness analysis for CF, the possibility of comparing the results with other competing interventions is limited, and the decision makers' R_c is unknown. Further studies are needed to assess the cost-effectiveness of new high-cost interventions in CF (for example, nebulised TOBI™, Chiron, USA). In order to facilitate comparison between interventions, future studies should use the same measures of cost-effectiveness.

One limitation of the study is the narrowness of the outcome measure used, which limits comparisons of cost-effectiveness with other studies evaluating therapies in CF or other lung diseases. The objective of the study was to provide decision makers with information on how best to allocate resources within this particular disease area rather than across a range of healthcare interventions. To facilitate broader comparisons a generic measure of outcome such as the QALY would have been needed. Whilst the study did collect information on QoL using a disease-specific measure, it was not possible to use this measure to derive QALY values.

The results of the study apply to a 12-week observation period. The duration of the study was insufficient to assess directly whether the treatment regimen had an effect on survival. This meant that any assessment of the impact of the interventions on survival would have relied on extrapolation. Such an extrapolation would have required data on the association of lung function with long-term survival. Whilst, more generally, such data are used in models for estimating the long-term cost-effectiveness of new interventions, the validity of the predictions depends on the quality of the data. Models which rely on poor quality data to make extrapolations of this kind have been criticised for producing invalid results. For this study, the lack of good quality longitudinal data available for extrapolating from the trial results, led us to limit the analysis to the 12-week observation period. However, as better quality epidemiological data become available, it would seem important to develop models which can be used to estimate the long-term cost-effectiveness of new interventions in this area.

This study is a rare example of a full economic evaluation alongside a crossover trial. This raised certain methodological issues, in particular with regard to the fact that all the results are based on paired differences within patients, which increases statistical efficiency. The method used to measure outcomes in the economic evaluation compared the between-treatment differences in outcome by subtracting the start-of-treatment FEV_1 from the end-of-treatment FEV_1, on a logged scale. This method adjusted for baseline values and provided results which could be used in the bootstrapping procedure required for the cost-effectiveness

analysis. In the trial, analysis of covariance was used to provide baseline-adjusted outcome measures, but could not so easily be used as a basis for a cost-effectiveness analysis. The different methods produced somewhat different estimates of incremental effectiveness.

Relevance to the NHS

In the UK, children with CF who have moderate to severe lung disease are routinely prescribed daily rhDNase. If decision makers were prepared to pay £200 for a 1% gain in FEV_1 (or £2000 for a 10% gain) over a 12-week period, then either rhDNase strategy, on average, has positive net benefits compared with HS and could be adopted.

This evaluation did not find that daily rhDNase improves patient lung function when compared with alternate-day rhDNase, and the total health service cost of alternate-day rhDNase was on average about £500 lower over 12 weeks. Assuming that the pattern of health service use was maintained over a year, moving to alternate-day rhDNase could lead to a reduction in annual health service costs of about £2000 per patient. Our results therefore suggest that providing rhDNase on an alternate-day basis may be the more cost-effective alternative. However, there is considerable uncertainty surrounding the estimates of cost and cost-effectiveness, which suggests that further work is required to establish that alternate-day rhDNase is definitely the more cost-effective option. Such a study could also examine the potentially reduced burden to the patient on alternate-day rhDNase who would need to take time-consuming nebulised medication less frequently.

Recommendations for future research

The study has shown the effects of the trial drugs on CF patients with moderate to severe lung disease. These drugs should now be assessed in patients with early-stage disease (FEV_1 greater than 80%). There was a marked variation in individual response to the treatments, and one subgroup of patients did not respond to any of the drugs. Further studies are needed to assess why this variation in response should occur. Rigorous clinical trials of other mucolytic drugs, such as mannitol, should be undertaken before their use is considered in patients who do not respond to current mucolytic therapies.

Any potential effects of the drugs on airway inflammation need to be studied, and in particular, any effects of HS on the activity of defensins and other salt-sensitive peptides in the CF airway. Such investigation is particularly important with regard to children with milder lung disease or in patients where chronic infection with *P. aeruginosa* has not occurred.

The cost saving of using alternate-day rhDNase in preference to daily rhDNase did not reach statistical significance in the study. A long-term parallel study comparing costs and outcomes between daily and alternate-day rhDNase is now required to provide an accurate economic evaluation of the cost savings involved. This study should cover the costs to the health service, the patients and their carers.

Conclusion

In conclusion, our study found that 7% HS does not appear to be as effective as daily rhDNase, although there was some variation in individual response. Alternate-day rhDNase appears to be as effective as daily rhDNase in CF. Administration of rhDNase on an alternate-day rather than a daily basis was equally effective, and on average reduced health service costs over a 12-week period. The cost-effectiveness analysis suggested that, on average, either rhDNase strategy is cost-effective. As alternate-day rhDNase has lower average costs, this may well prove to be the most cost-effective option.

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Appendix 1

Resource-use checklist for use in interviews

Each section is to be completed for each study centre.

Section 1: general information

(To be completed by lead clinical investigator/information department.)

(All answers should relate to period of study 1999–2000, or most recent financial year for which figures are available.)

- Total number of beds in hospital.
- Speciality within which CF patients are treated.
- Number of beds in above speciality.
- Number of beds in ward where CF patients are treated.
- Number of beds in specific area where CF patients have inpatient care.
- Description of area where CF patients may come for:
  - day-case care (speciality, ward area if applicable)
  - outpatient department (speciality, ward area if applicable).

Section 2: inpatient care

(Only relates to inpatient care, must exclude day-case, outpatient care)

Doctors

- Number of doctors (by grade, senior house officer/specialist registrar, consultant, etc.) covering the inpatient ward on which CF patients are treated.
- The number of sessions per week for which these doctors will be on the ward (exclude time in outpatient clinic/dealing with day cases).
- The additional coverage for 'on call time': the amount of time per week the doctors are on call for, where they are based during that time and the total number of beds they are usually covering during that time.
- How many hours in total do these doctors work per week, how many weeks' holiday do they have per year?

Nurses

- Total number of nurses working in relevant care area (either ward or sub ward CF area).

Please complete the following grid:

Monday–Friday

	Shift times (e.g. 8 am–4 pm)	Number of nurses grade D and above	Number of nurses grade C and below
AM			
PM			
Night			

Saturday–Sunday

	Shift times (e.g. 8 am–4 pm)	Number of nurses grade D and above	Number of nurses grade C and below
AM			
PM			
Night			

- How many hours per week do the nurses work as part of normal, contracted time, overtime?
- What arrangements exist for overtime, extra money each month, days off in lieu?
- How many days' holiday each year do the nurses have?

Other healthcare professionals

- How many times on average would a physiotherapist see a patient with CF during, say, an average 2-week hospital stay?
- How many times on average would a dietician see a patient with CF during, say, an average 2-week hospital stay?
- How many times on average would a psychologist see a patient with CF during, say, an average 2-week hospital stay?
- How many times on average would a social worker see a patient with CF during, say, an average 2-week hospital stay?
- How many secretaries/support staff work directly on the ward relevant to CF patients?

Section 3: day cases

- Where would a patient be seen as a day case? (On ward/separate area, A&E etc?)
- Typically for how long would a patient be attending the ward during a day-case visit (number of hours/mins)?
- For how long would the designated nurse be supervising the patient during the appointment?
- How many nurses are working solely with day-case patients?
- How many days per week does the day-case service run?
- Please estimate on average the proportion of day-case CF patients who see each healthcare professional and the average duration of the consultation.

	% day cases seen e.g. 80%	Duration of consultation e.g. 30 minutes
Doctor		
Dietician		
Physiotherapy		
Social worker		
Psychologist		
Other (please specify)		

What proportion of day-case patients would see a consultant or a specialist registrar?

- How many secretaries/support staff work in day-case care for CF/other patients in the same area?

Section 4: outpatient clinic

- For the outpatient clinic, please could you again estimate the proportion of CF patients who would be seen by each of the following healthcare professionals.

	% day cases seen e.g. 80%	Duration of consultation e.g. 30 minutes
Nurse		
Doctor		
Dietician		
Physiotherapy		
Social worker		
Psychologist		
Other (please specify)		

- Is there a special outpatient clinic for patients with CF or is the CF clinic part of a more general respiratory/paediatric clinic?
- How many doctors (of each grade) cover the outpatient clinic?
- How many nurses, of each grade, cover the outpatient clinic?
- How long (number of hours) would an outpatient clinic usually last?
- How much secretary/support staff time would be involved in the outpatient clinic?
- How many patients (all types) would usually be seen during the outpatient session?

Appendix 2

Unit costs used in cost analysis

TABLE 16 *Unit costs (£) of blood tests for each study centre*

	Study centre		
	1	2	3
Blood tests			
Full blood count	3.70	4.47	1.88
Urea and electrolytes	4.40	2.00	0.61
Liver function test	4.40	2.00	1.22
Urine – albumin	1.50	NA	NA
Urine – creatinine	1.50	NA	NA
Bone profile	4.40	2.00	2.43
Glucose	1.70	1.00	0.61
Immunoglobin G (IgG)	8.50	5.00	8.00
Immunoglobin A (IgA)	8.50	5.00	8.00
Immunoglobin M (IgM)	8.50	5.00	8.00
Immunoglobin E (IgE)	8.50	5.00	8.00
IgA, IgM + IgE	9.70	15.00	8.00
Clotting screen	13.60	2.96	10.00
Viral serology	28.50	12.00	28.50
Aspergillus radioallergosorbent test (RAST)	11.10	9.00	NA
Aspergillus precipitans	22.20	10.00	NA
Atypical pneumonia screen	28.50	10.00	NA
C-reactive protein	6.50	2.00	1.48
Erythrocyte sedimentation rate (ESR)	3.70	1.34	1.83
Blood culture	11.80	10.00	17.86
Glycosylated haemoglobin	4.70	4.00	1.96
Cholesterol	1.10	3.00	1.30
Triglycerides	1.10	3.00	0.61
Testosterone level	21.40	7.00	NA
Vitamin A level	17.80	12.00	NA
Vitamin E level	17.80	12.00	NA
Vitamin D level	45.10	12.00	NA
Iron	1.90	2.00	NA
Total iron-binding capacity (TIBC)	3.70	3.00	NA
3-day faecal fat	NA	20.00	NA
Group & save	9.30	8.04	5.24
Cross-match	9.80	9.91	4.59
Anti-streptolysin-O (ASO) titre	13.10	NA	NA
Anti-DNAse B titre	13.90	NA	NA
Anti-nuclease antibody	11.60	NA	NA
Anti-staphylolysin antibody	13.10	NA	NA
Haemoglobin electrophoresis	5.60	NA	5.60
Amikacin level	23.50	15.00	15.00
Gentamicin level	23.50	15.00	15.00
Tobramycin level	23.50	15.00	15.00
Bronchoalveolar lavage	18.30	10.00	NA

NA, not applicable as test not performed, or cost not available in the centre concerned

TABLE 17 *Unit costs (£) of radiological investigations and procedures for each study centre*

	Study centre		
	1	**2**	**3**
Radiological investigations			
Chest X-ray	29.40	31.00	24.00
Abdominal X-ray	29.40	31.00	24.00
C spine X-ray	36.70	36.00	46.00
Thoracic spine X-ray	36.70	36.00	46.00
Lumbar spine X-ray	36.70	36.00	46.00
Abdominal ultrasound	99.20	77.00	46.00
Echocardiogram	150.00	113.00	113.00
Barium swallow	89.70	93.00	92.00
CT scan: chest	266.00	278.00	152.00
CT scan: abdomen	266.00	278.00	152.00
Ventilation scan	287.50	206.00	92.00
Ventilation scan/perfusion (V/Q) scan	460.90	340.00	NA
Hand X-ray	29.40	NA	NA
Sinus X-ray	36.70	NA	NA
Spinal bone density scan	NA	144.00	NA
Ventilation–perfusion scan	460.90	NA	NA
Annual assessment investigations	152.50	148.77	NA
Procedures			
Gastrostomy	722.91	NA	NA
Portacath	722.91	72.00	NA
Bronchoscopy	481.94	315.00	NA

NA, not applicable as test not performed, or cost not available in the centre concerned

TABLE 18 *Unit cost of community services (adapted from Netten* et al., *1999*[167]*)*

	Cost (£)
Service	
GP home visit	50.47
GP clinic visit	22.66
Community nurse home visit	10.30
Community nurse clinic visit	7.81
Physiotherapist home visit	37.08
Physiotherapist clinic visit	13.39

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We look forward to hearing from you.

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