National Institute for Health and Care Excellence

D Version 1.0 Pre-consultation

Cystic Fibrosis: diagnosis and management

Appendix L

Main appendix document

Health economics evidence tables

04 May 2017

Draft for Consultation

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologist

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Appendices

Appendix L: Health economics evidence tables

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Full citation Thornton, J., Elliott, R. A., Tully, M. P., Dodd, M., Webb, A. K., Clinical and economic choices in the treatment of respiratory infections in cystic fibrosis: comparing hospital and home care, Journal of Cystic Fibrosis, 4, 239-47, 2005 **Ref Id** 363119 **Economic study type** Cost-effectiveness analysis	**Study dates** September 2000 to September 2001 **Intervention** Home IV antibiotics: >60% of antibiotic courses undertaken at home (n=47) **Comparison(s)** Hospital IV antibiotics: >60% antibiotic courses undertaken in hospital (n=51) Both: the remaining patients who received 40–60% of IV antibiotic treatment at home or in hospital (n=18)	**Source of effectiveness data** Retrospective, observational, 1-year study for respiratory exacerbations in adults with CF (not limited to P. aeruginosa lung infection). Mean age 26 years (range 16 to 47). **Source of cost data** • Unit costs were calculated from the NHS Trust, the CF Unit budget, the BNF and the hospital-supplied catalogue • Resource use and costs were estimated for i.v. antibiotics, disposable equipment, home kits, sputum microbiology, and sensitivity and blood drug level assays • The time spent with	**Time horizon and discount rate** • Time horizon: 1 year • Discount rate: NA **Method of eliciting health valuations (if applicable)** NA **Modelling approach** NA	**Cost per patient per alternative** <u>Mean (95% CI) over the 1 year study period: home; hospital</u> • Antibiotics: £9,325 (£6,853 to £11,797); £7,920 (£5,514 to £10,327) • Home kits: £39 (£33 to £45); £8 (£4 to £13) • Lab tests: £88 (£68 to £107); £113 (£91 to £135) • Clinic visits: £789 (£648 to £929); £268 (£204 to £332) • Days in hospital: £3,263 (£1,966 to £4,560); £14,299 (£11,430 to £17,167) • Home visits: £25 (£1 to £87); £0 • Total: £13,528 (£9,989 to £17,068); £22,609 (£17,648 to £27,569) The total cost per hospital course was statistically significantly higher than cost per home course: mean difference £2,836 (£2,151 to £3,522, p<0.001). The costs of courses where effectiveness data were missing were subtracted from the total costs of treatment, the re-calculated mean costs per course of antibiotics were £3,223 for home care and £6,060 for hospital care.	**Limitations** • Not a randomised controlled trial so there may be differences in groups that have not been controlled for, although the authors report that there were no differences in patient characteristics or FEV1% at the start of the study. • Unclear if all CF related care has been captured • Hospital transport reported to be used by some patients, but this has not been costed

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Country(ies) where the study was done UK **Perspective & Cost Year** UK NHS perspective. Cost year 2002. **Source of funding** Carried out as part of a phD project funded by the School of Pharmacy and Pharmaceutical Sciences, University of Manchester.		each patient was estimated using a time sheet completed by each staffmember attending the patient • Staff costs were obtained from the CF Unit budget • Clinical records were used to determine the number of days patients spent in hospital relating to i.v. antibiotic treatment • Fixed costs for the ward and outpatient clinic were calculated from the CF Unit budget; these were used to estimate a fixed cost per hour related to an inpatient stay or clinic visit • A standard time per home visit was determined by interviewing staff • Travel time from the clinic to each patient's home was estimated using data from the Automobile Association • The cost of travel for each home visit was calculated using a standard mileage allowance obtained from		**Effectiveness per patient per alternative** <u>Effectiveness at the end of the 1 year study period compared with baseline "average" FEV1</u> <u>n (%): home; hospital</u> • Base case ≤0% decline: 20 (42.6%); 30 (58.8%) • ≤2% decline: 20 (42.6%); 32 (62.7%) <u>Treatment courses</u> • Improvement in FEV1 from the baseline "best" was statistically significantly higher for hospital-based patients than home-based (mean difference 4.6%, 95% CI 1.8% to 7.4%; p=0.001) • Hospital-based patients had statistically significantly more courses of treatment in which lung function was maintained at baseline "average" (FEV1 ≤0%) than home-based patients (17.4% compared with 9.0%; p=0.001) <u>Effectiveness (%) used to calculate ICERs: home; hospital</u> • Base case ≤0% decline: 42.6; 58.8 • ≤2% decline: 42.6; 62.7 **Incremental cost-effectiveness** <u>Mean ICER (95% CI)</u> • Base case ≤0% decline: £46,098 (£17,300 to £113,478)	**Other information** • Home care IV in this study is not provided by contracted home-care companies • For travel to outpatient clinic appointments at the start of antibiotic treatment, 60% of home patients used their own car, 33% had a lift from family or friends and 7% used hospital transport • When admitted, 29% used their own car, 53% had a lift from family or friends, 3% used a taxi and 12% used hospital transport.

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		the hospital payroll department **Other data sources e.g. transition probabilities** NA		• ≤2% decline: £73,885 (1,236 to £269,023) • These are the amounts that must be spent to obtain one more year of effective treatment with hospital care for one patient <u>Bootstrap ICER (2.5th and 97.5th percentiles)</u> • Base case ≤0% decline: £10,923 (-£221,078 and £199,978) • ≤2% decline: £12,878 (-£231,167 and £262,204) **Other reporting of results** • In the cost-effectiveness plane, most data points were located in the north-east plane, indicating increased effectiveness and increased cost • Hospital-based care may be cost-effective with a 95% probability at a willingness to pay of £262,500 for one extra patient with a decline in FEV1 of≤2% • However, using a stricter definition of lung function (decline in FEV1 of ≤0%) the probability that hospital-based care is cost-effective at a willingness to pay of £10M per patient is <0.05 **Uncertainty** • Treatment was defined as effective if lung function was maintained at the baseline 'best' FEV1 level, i.e. percentage decline in FEV1 was ≤0% and an additional analysis with a less stringent definition of effectiveness of percentage decline in FEV1 of ≤2% was also performed	

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				• Cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) were also presented	
Full citation Etherington, C., Hall, M., Conway, S., Peckham, D., Denton, M., Clinical impact of reducing routine susceptibility testing in chronic Pseudomonas aeruginosa infections in cystic fibrosis, Journal of Antimicrobial Chemotherapy, 61, 425-7, 2008 **Ref Id** 330772 **Economic study type** Cost consequence analysis **Country(ies) where the study was done** UK	**Study dates** 6 month period between June and November 2006 compared to the same calendar months in 2005 **Intervention** Introduced a protocol in 2006 whereby susceptibility tests of P. aeruginosa isolates obtained from respiratory samples of people with CF were limited to those taken at the commencement of antibiotic therapy, when there was evidence of clinical failure of therapy or routinely if not tested in the previous 3 months **Comparison(s)**	**Source of effectiveness data** 193 study participants from The Microbiology Department of the Leeds Teaching Hospitals NHS Trust **Source of cost data** Not reported **Other data sources e.g. transition probabilities** NA	**Time horizon and discount rate** • Time horizon: 6 months • Discount rate: NA **Method of eliciting health valuations (if applicable)** NA **Modelling approach** NA	**Cost per patient per alternative** The projected savings of this intervention were €3,500 in consumables (media, antibiotic discs and sundries) and 170 hours (costed at €6,500) of laboratory staff time per annum, a total annual saving of €10,000 (£6500). **Effectiveness per patient per alternative** No significant differences in median change of FEV1, FVC, C-reactive protein (CRP), white cell count, weight or duration of intravenous antibiotics were observed. <u>Change from start of treatment 2005 median (range) (95% CI); 2006 median (range) (95% CI); P value</u> • FEV1 (L): 0.13 (20.52 to 1.28) (0.10, 0.16); 0.13 (20.56 to 1.26) (0.10, 0.17); 0.897 • FVC (L): 0.26 (20.90 to 2.09) (0.18, 0.31); 0.23 (20.7 to 2.98) (0.16, 0.29); 0.939 • CRP (mg/L): 25.85 (2266.0 to 102.70) (27.90, 21.70); 25.25 (2189.0 to 47.0) (27.31, 22.01); 0.589 • WCC (109 /L): 21.53 (214.2 to 6.08) (21.92, 21.02); 21.54 (219.6 to 8.91) (21.89, 21.17); 0.431 • Weight (kg): 0.20 (23.5 to 6.7) (0.1, 0.25); 0.23 (24.3 to 7.45) (0.15, 0.51); 0.431 • Number of days of intravenous antibiotics 14 (2–68) (13, 16); 14 (8–55) (14, 14); 0.168	**Limitations** • Cost sources and resource use not reported • The number of times samples were taken when there was evidence of clinical failure of therapy not reported • Uncertainty not assessed **Other information**

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Perspective & Cost Year Perspective: NHS Cost year: 2006 **Source of funding** None	Sputum samples would be collected at each clinic visit and at the beginning and end of every course of intravenous antibiotics. This approach is consistent with the UK's Cystic Fibrosis Trust recommendations that respiratory samples should be obtained every 4 – 8 weeks.			**Incremental cost-effectiveness** Not reported **Other reporting of results** The application of the new protocol reduced the number of susceptibility tests by 56% (from a projected 2,231 tests on 872 samples to an actual 972 tests on 427 samples) **Uncertainty** Not assessed	
Full citation Tappenden,P., Harnan,S., Uttley,L., Mildred,M., Carroll,C., Cantrell,A., Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of chronic Pseudomonas aeruginosa lung infection in cystic fibrosis:	**Study dates** COLO/DPI/02/06 study dates not reported but the last patient visit was performed in August 2014. Forest laboritories submission published in 2011. Assessment report accepted for publication in November 2011. **Intervention**	**Source of effectiveness data** 24 week transition probabilities between FEV1 states, exacerbation rates, baseline age and initial FEV1 distributions were estimated from a prospective, randomised, open-label, non-inferiority, phase III clinical trial. Within the COLO/DPI/02/06 (FREEDOM) trial 380 patients randomised to receive colistimethate sodium DPI (125mg twice daily) or three alternating cycles of 28 days with then	**Time horizon and discount rate** • Time horizon: 1. reference case analysis based on FEV1 extrapolation over a lifetime horizon; 2. 'within-trial' analysis that does not include any extrapolation • Discount rate:	**Cost per patient per alternative** <u>Reference case model, probabilistic</u> *Coli DPI acquisition cost*; Coli DPI total cost vs. NT total cost; Inc • *£9.11*; £93,916 vs. £110,519; -£16,603 • *£10.60*; £107,391 vs. £110,519; -£3,128 • *£15.98*; £156,045 vs. £110,519; £45,527 • *£19.64*; £189,145 vs. £110,519; £78,626 • *£21.20*; £203,253 vs. £110,519; £92,734 • *£39.29*; £366,852 vs. £110,519; £256,334 <u>'Within-trial' model, probabilistic</u> *Coli DPI acquisition cost*; Coli DPI total cost vs. NT total cost; Inc	**Limitations** • The model does not include treatment related adverse events even though the incidence was higher for colistimethate sodium DPI than NT • No treatment was not included as a treatment arm in the trials and model

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
systematic review and economic model, Health Technology Assessment (Winchester, England), 17, v-xvii, 2013 **Ref Id** 322218 **Economic study type** Cost utility analysis **Country(ies) where the study was done** COLO/DPI/02/06 trial undertaken in 66 centres in EU countries in Russia and Ukraine **Perspective & Cost Year** NHS non-societal perspective. Cost year 2011/12.	Nebulised tobramycin (NT) **Comparison(s)** Colistimethate sodium dry powder inhalation (DPI). In addition a crude threshold analysis is presented to compare tobramycin DPI with NT.	28 days without NT (300mg/5ml twice daily) over a period of 24 weeks **Source of cost data** • Exacerbation costs (minor, £403; major, £1,500) were taken from NHS Reference Costs using asthma complications as a proxy • Drug acquisition costs for NT were taken from the BNF62, this corresponded to a price per dose of £21.20 • For colistimethate sodium DPI Forest Laboratories provided a price of £17.30 per dose, but a price range of £9.11 to £39.29 per dose over six scenarios is presented • Nebuliser costs of £200 (SE £10) per year to cover replacement heads and filters assumed from personal communications with a Physician **Other data sources e.g.**	3.5% • Cycle length: 24 weeks **Method of eliciting health valuations (if applicable)** COLO/DPI/02/06 trial did not included a preference-based measure of HRQoL, hence a systematic review of the literature was undertaken. The following HRQoL parameters were taken from Bradley et al. where 94 CF patients ≥16 years with chronic *P.aeruginosa* completed the EQ-5D • Disutility major exacerbations 0.17 • Disutility minor exacerbations 0.02 • Utility FEV1 ≥70% 0.86 • Utility FEV1 40-69% 0.81	• £9,11; £3,469 vs. £4,075; -£606 • £10.60; £3,967 vs. £4,075; -£109 • £15.98; £5,764 vs. £4,075; £1,688 • £19.64; £6,986 vs. £4,075; £2,911 • £21.20; £7,507 vs. £4,075; £3,432 • £39.29; £13,550 vs. £4,075; £9,475 **Effectiveness per patient per alternative** <u>Reference case model, QALYs gained, probabilistic</u> • Coli DPI 9.48 • NT 9.6 • Inc (Coli DPI vs. NT) -0.13 <u>'Within-trial' model, QALYs gained, probabilistic</u> • Coli DPI 0.35 • NT 0.35 • Inc (Coli DPI vs. NT) -0.00 **Incremental cost-effectiveness** <u>Reference case model, probabilistic</u> *Coli DPI acquisition cost*; ICER (Coli DPI vs. NT) • *£9*.11; £126,259 in the south-west quadrant reflecting a QALY loss and cost saving for Coli DPI vs. NT • £10.60; £23,788 in the south-west quadrant reflecting a QALY loss and cost saving for Coli DPI	**Other information** • FEV1 and exacerbations are assumed not to impact survival in the model, this is reportedly due to a lack of evidence • The authors note that the model does not include the potential impact of resistance to tobramycin

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Source of funding NIHR HTA programme		**transition probabilities** • Age-specific survivor functions for CF patients were estimated from Dodge et al. using a Weibull function, but no difference in survival is assumed between competing treatments • The probability of patients with FEV1 <40% undergoing a lung transplant was assumed to be 3%, based on data from the UK CF Registry and the US CF Foundation, this probability is also assumed to be independent of age	• Utility <40% 0.64 Utility post lung transplantation (0.83) taken from Anyanwu et al. 2001 where 255 transplant recipients attended follow up clinics completed the EQ-5D(further utility decrements relating to exacerbations were not applied to these patients). **Modelling approach** Markov state transition model, health states include: • FEV1 ≥70% • FEV1 40-69% • FEV1 <40% • Post lung transplantation • Death Adverse events were not included. Exacerbations were not included as a separate health state, instead a proportion of patients in the	vs. NT • £15.98; NT dominates Coli DPI • £19.64; NT dominates Coli DPI • £21.20; NT dominates Coli DPI • £39.29; NT dominates Coli DPI 'Within trial' model, probabilistic *Coli DPI acquisition cost*; ICER (Coli DPI vs. NT) • *£9.11*; £276,814 in the south-west quadrant reflecting a QALY loss and cost saving for Coli DPI vs. NT) • £10.60; £49,596 in the south-west quadrant reflecting a QALY loss and cost saving for Coli DPI vs. NT) • £15.98; NT dominates Coli DPI • £19.64; NT dominates Coli DPI • £21.20; NT dominates Coli DPI • £39.29; NT dominates Coli DPI **Other reporting of results** Simple sensitivity analysis The results were particularly sensitive to Yi et al. utility values, leading to positive ICERs that were previously dominated. Tobi DPI vs. NT Given the incremental cost of DPI, Tobi DPI would have to produce 1.54 (2.31) additional discounted QALYs compared with NT to achieve a cost-utility ratio of £30,000 (£20,000) per QALY gained. Further analyses of both Coli DPI, Tobi DPI and NT including patient access schemes was undertaken by Tappenden et al.	

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			FEV1 health states experienced an exacerbation associated with a treatment cost and disutility.	**Uncertainty** Simple sensitivity analysis was undertaken for the lifetime model for each of the six Coli DPI prices including: • Point estimates of parameters rather than expectations of the mean • Using alternative utility values for FEV1 reported by Yi et al. and Stah et al. • FEV1 transition probabilities for the nebulised tobramycin group set equal to the colistimethate DPI group • Disutility for exacerbations was doubled • Major exacerbation was doubled PSA was also performed over 5,000 samples and cost effectiveness acceptability curves are presented for both time horizons at each of the six Coli CPI costs per dose. A validation exercise was undertaken to examine the plausibility of the extrapolated Markov trace based on the COLO/DPI/02/06 trial by deriving equivalent transition matrices using longitudinal panel data from the CF Registry 1997-2008.	
Full citation Elliott, R. A., Thornton, J., Webb, A. K., Dodd, M., Tully, M. P., Comparing costs of home- versus hospital-based treatment of infections in	**Study dates** September 2000 - September 2001 **Intervention** Home IV antibiotics: >60% of antibiotic	**Source of effectiveness data** Retrospective, observational, 1-year study for respiratory exacerbations in adults with CF (not limited to P. aeruginosa lung infection). Mean age 26 years (range 16 to 47).	**Time horizon and discount rate** • Time horizon: 1 year • Discount rate: NA	**Cost per patient per alternative** <u>Mean (95% CI) over the 1 year study period</u> Home; hospital • Antibiotics: £9,325 (£6,853 to £11,797); £7,920 (£5,514 to £10,327) • Home kits: £39 (£33 to £45); £8 (£4 to £13) • Lab tests: £88 (£68 to £107); £113 (£91 to £135) • Clinic visits: £789 (£648 to £929); £268 (£204 to	**Limitations** • Not a randomised controlled trial so there may be differences in groups that have not been controlled for, although the

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
adults in a specialist cystic fibrosis center, International Journal of Technology Assessment in Health Care, 21, 506-10, 2005 **Ref Id** 363146 **Economic study type** Cost-consequence analysis **Country(ies) where the study was done** UK **Perspective & Cost Year** UK NHS perspective. Cost year 2002. **Source of**	courses undertaken at home (n=47) **Comparison(s)** Hospital IV antibiotics: >60% antibiotic courses undertaken in hospital (n=51) Both: the remaining patients who received 40–60% of IV antibiotic treatment at home or in hospital (n=18)	**Source of cost data** • Unit costs were calculated from the NHS Trust, the CF Unit budget, the BNF and the hospital-supplied catalogue • Resource use and costs were estimated for i.v. antibiotics, disposable equipment, home kits, sputum microbiology, and sensitivity and blood drug level assays • The time spent with each patient was estimated using a time sheet completed by each staffmember attending the patient • Staff costs were obtained from the CF Unit budget • Clinical records were used to determine the number of days patients spent in hospital relating to i.v. antibiotic treatment • Fixed costs for the ward and outpatient clinic were calculated from the CF Unit budget; these were used to	**Method of eliciting health valuations (if applicable)** NA **Modelling approach** NA	£332) • Days in hospital: £3,263 (£1,966 to £4,560); £14,299 (£11,430 to £17,167) • Home visits: £25 (£1 to £87); £0 • Total: £13,528 (£9,989 to £17,068); £22,609 (£17,648 to £27,569) The total cost per hospital course was statistically significantly higher than cost per home course: mean difference £2,836 (£2,151 to £3,522, p<0.001) **Effectiveness per patient per alternative** Reported in Thornton et al. 2005 **Incremental cost-effectiveness** NA **Other reporting of results** NA **Uncertainty** 95% CIs reported	authors report that there were no differences in patient characteristics or FEV1% at the start of the study • Unclear if all CF related care has been captured **Other information** Home care IV in this study is not provided by contracted home-care companies

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funding Carried out as part of a phD project funded by the School of Pharmacy and Pharmaceutical Sciences, University of Manchester.		estimate a fixed cost per hour related to an inpatient stay or clinic visit • A standard time per home visit was determined by interviewing staff • Travel time from the clinic to each patient's home was estimated using data from the Automobile Association • The cost of travel for each home visit was calculated using a standard mileage allowance obtained from the hospital payroll department **Other data sources e.g. transition probabilities** NA			
Full citation Tappenden, P., Harnan, S., Uttley, L., Mildred, M., Walshaw, M., Taylor, C., Brownlee, K., The cost effectiveness of dry powder antibiotics for the	**Study dates** EAGER trial published by Konstan et al. 2011. FREEDOM trial published by Schuster et al. 2012.	**Source of effectiveness data** 24 week transition probabilities between FEV1 states, baseline age and initial FEV1 distributions were estimated from two prospective, randomised, open-label, non-inferiority, phase III	**Time horizon and discount rate** • Time horizon: lifetime • Discount rate: 3.5% • Cycle length: 24 weeks	**Cost per patient per alternative** *List price* Coli DPI vs. NT; Inc £167,983 vs. £110,519; £57,464 Tobi DPI vs. NT; Inc £136,965 vs. £94,512; £42,453 *PAS price* Coli DPI vs. NT; Inc £72,572 vs. £110,519; -£37,946	**Limitations** • Adverse events are not included in the model even though incidence data is reported • No treatment was not included as a treatment arm in

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
treatment of Pseudomonas aeruginosa in patients with cystic fibrosis, Pharmacoeconomics, 32, 159-72, 2014 **Ref Id** 332117 **Economic study type** Cost utility analysis **Country(ies) where the study was done** Not reported **Perspective & Cost Year** NHS non-societal perspective. Cost year 2011/12. **Source of funding**	**Intervention** Nebulised tobramycin (NT) **Comparison(s)** • Colistimethate sodium dry powder inhalation (DPI) • Tobramycin DPI	clinical trials: FREEDOM 380 patients randomised to receive colistimethate sodium DPI (125mg twice daily) or three alternating cycles of 28 days with then 28 days without NT (300mg/5ml twice dailu) over a period of 24 weeks EAGER 553 patients randomised to receive tobramycin DPI (112mg twice daily) or NT (300mg/5ml twice daily) over three 28-day cycles over a period of 24 weeks **Source of cost data** Exacerbation costs were taken from NHS Reference Costs using asthma complications as a proxy: • Minor £403 • Major £1,500 Drug acquisition costs taken from the BNF62 corresponding to a price per dose of: • NT £21.20 • tobramycin DPI £31.96	**Method of eliciting health valuations (if applicable)** Neither of the pivotal trials included a preference-based measure of HRQoL, hence a systematic review of the literature was undertaken. The following HRQoL parameters were taken from Bradley et al. where 94 CF patients ≥16 years with chronic *P.aeruginosa* completed the EQ-5D • Disutility major exacerbations 0.17 • Disutility minor exacerbations 0.02 • Utility FEV1 ≥70% 0.86 • Utility FEV1 40-69% 0.81 • Utility <40% 0.64 Utility post lung transplantation (0.83) taken from Anyanwu	Tobi DPI vs. NT; Inc £75,237 vs. £94,512; -£19,275 **Effectiveness per patient per alternative** QALYs gained Coli DPI vs. NT; Inc 9.48 vs. 9.61; -0.13 Tobi DPI vs. NT; Inc 8.73 vs. 8.38; 0.34 **Incremental cost-effectiveness** *List price* Coli DPI vs. NT NT dominates coli DPI Tobi DPI vs. NT £123,563 *PAS price* Coli DPI vs. NT £288,563 in the south-west quadrant of the cost-effectiveness plane (incremental effect on health is negative with cost savings) Tobi DPI vs. NT Tobi DPI dominates NT	the trials and model **Other information** • The structure of the model is equivalent to that reported in Tappenden et al. this publication follows the additional analyses proposed by the assessment group for NT vs. tobramycin DPI • FEV1 and exacerbations are assumed not to impact survival in the model, this is reportedly due to a lack of evidence

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
NIHR HTA programme		• colistimethate sodium DPI £17.30 Nebuliser costs of £200 from personal communications with a Physician **Other data sources e.g. transition probabilities** • Age-specific survivor functions for CF patients were estimated from Dodge et al. using a Weibull function, but no difference in survival is assumed between competing treatments • The probability of patients with FEV1 <40% undergoing a lung transplant was assumed to be 3%, based on data from the UK CF Registry and the US CF Foundation, this probability is also assumed to be independent of age	et al. 2001 where 255 transplant recipients attended follow up clinics completed the EQ-5D (further utility decrements relating to exacerbations were not applied to these patients). **Modelling approach** Markov state transition model, health states include: • FEV1 ≥70% • FEV1 40-69% • FEV1 <40% • Post lung transplantation (further utility decrements relating to exacerbations were not applied to these patients) • Death Adverse events were not included. Exacerbations were not included as a separate health state, instead a proportion	**Other reporting of results** <u>PSA</u> Assuming a willingness-to-pay threshold of £20,000 per QALY gained: • Based on the list prices, the probability that tobramycin DPI or colistimethate sodium DPI produce more net benefit than NT is approximately zero • Based on the proposed PAS prices, the probability that tobramycin DPI and colistimethate sodium DPI produce more net benefit than NT is approximately zero <u>Simple sensitivity analysis, list price</u> • Scenarios using Yi et al. utility values or equal FEV1 trajectories resulted in positive ICERs (<£30,000) for Coli DPI vs. NT (in all other scenario NT dominated Coli DPI as in the base-case) • The scenario using equal FEV1 trajectories resulted in NT dominating Tobi DPI (in all other scenario Tobi DPI had a positive ICER >£100,000 vs. NT similar to the base-case) **Uncertainty** Included additional analyses of PAS discounts offered by the manufacturers for both DPI products. Simple sensitivity analysis was undertaken including:	

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			of patients in the FEV1 health states experienced an exacerbation associated with a treatment cost and disutility. In the base case a constant treatment effect beyond the pivotal trials was assumed.	• Restricting the time horizon to the "within-trial" 24 week period • Reducing the baseline age to 6 years • Point estimates of parameters rather than expectations of the mean • Using alternative utility values for FEV1 reported by Yi et al. and Stah et al. • FEV1 transition probabilities for the nebulised tobramycin group set equal to DPI groups • Disutility for exacerbation ±20% • Major exacerbation cost ±20% PSA was also performed and cost effectiveness acceptability curves are presented for both the list price and the PAS price scenarios.	
Full citation Grieve, R., Thompson, S., Normand, C., Suri, R., Bush, A., Wallis, C., A cost-effectiveness analysis of rhDNase in children with cystic fibrosis, International Journal of Technology Assessment in Health Care, 19, 71-9, 2003	**Study dates** Not reported. **Intervention** Daily 2.5 mg rhDNase. Alternate day 2.5mg rhDNase. **Comparison(s)** Hypertonic saline (HS)	**Source of effectiveness data** • A prospective, open, randomised, crossover trial in completed by 43 children aged 5 to 18 years, said to be described by Suri et al. 2002. • For each treatment period, the change in effectiveness was calculated by taking the natural logarithm of the end of the treatment FEV (yD, yA, yS) and beginning of treatment FEV (xD, xA, xS) for	**Time horizon and discount rate** • Time horizon: 12 weeks • Discount rate: NA **Method of eliciting health valuations (if applicable)** NA **Modelling approach** NA	**Cost per patient per alternative** <u>Total cost over 12 weeks, mean (SD)</u> • HS, £4,285 (£3,903) • Daily rhDNase, £5,694 (£3,377) • Alternate day rhDNase, £5,230 (£3,737) <u>Mean incremental cost (95% CI)</u> • Daily rhDNase - HS, £1,409 (£354 to £2,277) • Daily - alternate day rhDNase, £464 (-£647 to £1,510) • Alternate day rhDNase - HS, £945 (-£509 to £2,301) **Effectiveness per patient per alternative**	**Limitations** Trial methods and patient characteristics not reported, but said to be described previously in Suri et al. 2002. **Other information** • With a ceiling ratio of £200 per 1% gain in FEV, the probability of daily or alternate rhDNase proving cost-effective, compared with HS,

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Ref Id 360206 **Economic study type** Cost-effectiveness analysis **Country(ies) where the study was done** UK **Perspective & Cost Year** Cost year 1999/2000. NHS non-societal perspective. **Source of funding** Funded by NHS Health Technology Assessment Programme.		daily rhDNase, alternate day rhDNase and HD. • The difference in log FEV was calculated for each treatment period and compared between treatments. • For example, the incremental effectiveness of daily vs. alternate was eD-A = (yD - xD) - (yA - xA) • The incremental effectiveness was calculated on a log scale, which enabled the results to be interpreted in terms of percentage differences in FEV **Source of cost data** • Hospital contacts (inpatient, outpatient, day case) radiological investigations, blood tests, drugs, and the use of community services (including community nurse, physiotherapist, and general practitioner) were recorded for each patient. • Unit costs of health services were collected		<u>Mean (SD) resource use and clinical outcomes over 12 weeks</u> HS; daily rhDNase; alternate day rhDNase • Hospital admissions: 0.53 (0.75); 0.63 (0.87); 0.80 (1.07) • Total inpatient days: 5.13 (8.84); 4.73 (7.73); 5.65 (7.70) • Outpatient visits: 1.23 (1.10); 0.93 (1.07); 0.83 (0.81) • GP contacts: 0.25 (0.49); 0.30 (0.61); 0.18 (0.38) • Nurse contacts: 2.70 (10.12); 1.75 (6.65); 2.38 (7.91) <u>Mean (95% CI) incremental effect (FEV)</u> • Daily rhDNase - HS, 14 (5 to 23) • Daily - alternate day rhDNase, 2 (-6 to 12) • Alternate day rhDNase - HS 12 (2 to 22) **Incremental cost-effectiveness** <u>£ per 1% gain in FEV</u> • Daily rhDNase - HS, £110 • Daily - alternate day rhDNase, £214 • Alternate day rhDNase - HS, £89 **Other reporting of results** Net benefits were calculated for each bootstrap sample for a range of ceiling ratios per 1% increase in FEV <u>£400 per 1% gain in FEV</u>	would be 0.91 and 0.88. • For the same ceiling ratio the probability of daily rhDNase being cost-effective compared with alternate day rhDNase is 0.49. • The sensitivity analysis did not find the results sensitive to the unit costs of hospital services, but changing the price of rhDNase was somewhat more important: the probability of daily rhNDase compared with alternate day rhDNase being cost-effective, with a ceiling of £200 per 1% gain in FEV rose from 49% to 59% as the price of rhDNase was reduced by 30%.

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
		at the 2 hospitals where patients were recruited from and a local DGH, drug costs were taken from the BNF, and community care costs from Netten et al. 1999. • Unit cost of rhDNase £20.39 per day; HS, £0.38 per day • For each treatment comparison, the incremental cost was calculated as the difference in total costs and refers to a 12-week period. **Other data sources e.g. transition probabilities** NA		• Daily rhDNase - HS, £3,725 (£585 to £6,701) • Daily - alternate day rhDNase, £403 (-£3,303 to £3,341) • Alternate day rhDNase - HS, £3,321 (-£116 to £6,976) <u>£200 per 1% gain in FEV</u> • Daily rhDNase - HS, £1,158 (-£621 to £2,842) • Daily - alternate day rhDNase, -£30 (-£2,091 to £1,576) • Alternate day rhDNase - HS, £1,188 (-£847 to £3,343) <u>£100 per 1% gain in FEV</u> • Daily rhDNase - HS, -£126 (-£1,293 to £1,041) • Daily - alternate day rhDNase, -£246 (-£1,596 to £909) • Alternate day rhDNase - HS, £121 (-£1,323 to £1,752) **Uncertainty** • Mean incremental costs and benefits was reported with 95% CIs calculated using nonparametric bootstrap methods. • Using 2,000 samples cost-effectiveness planes and CEACs are presented. • Scenario reducing the price of rhNDase reported by the BNF by 10-30%.	

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Full citation McIlwaine, M. P., Richmond, M., Agnew, J. L., Alarie, N., Lands, L., Chilvers, M., Ratjen, F., Cost-effectiveness of performing positive expiratory pressure versus high frequency chest wall oscillation, Journal of Cystic Fibrosis, 13, S11, 2014 **Ref Id** 361466 **Economic study type** Cost-consequence analysis **Country(ies) where the study was done** Canada **Perspective &**	**Study dates** Not reported **Intervention** HFCWO **Comparison(s)** PEP mask	**Source of effectiveness data** RCT was performed in 12 CF centres over a one year period, 42 patients were randomised to PEP and 46 to HFCWO **Source of cost data** Services costed include the equipment (PEP, $75; HFCWO, $14,000), number of hospital days ($1,120 per day), antibiotic treatment either IV, inhaled, or oral, and number of days on home IV ($500 per day). Cost sources are not reported. **Other data sources e.g. transition probabilities** NA	**Time horizon and discount rate** • Time horizon: 1 year • Discount rate: NA **Method of eliciting health valuations (if applicable)** NA **Modelling approach** NA	**Cost per patient per alternative** Total treatment cost per patient for 1 year: • PEP $2,770 • HFCWO $6,419 Total medical cost per patient (including equipment cost) for 1 year: • PEP $2,845 • HFCWO $20,419 **Effectiveness per patient per alternative** <u>Exacerbations over 1 year:</u> • PEP 130 • HFCWO 369 **Incremental cost-effectiveness** Not reported **Other reporting of results** Costs and number of exacerbations disaggregated by services (i.e. antibiotic route, total number of hospital days and total number of days on home IV) **Uncertainty**	**Limitations** • Absence of detail regarding: cost build up for HFCWO equipment, specific sources of cost data, definition of an exacerbation, perspective and study dates. As such claims in this study cannot be verified. • Data in the paper is based on single values, there are no confidence intervals or measures of dispersion. • The cost of HFCWO equipment has not been annuitized over the equipment lifespan which over estimates the cost of the vest over one year.

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Cost Year Non-societal, NHS **Source of funding** Not reported				Not assessed	**Other information**
Full citation Moodie, M., Lal, A., Vidmar, S., Armstrong, D. S., Byrnes, C. A., Carlin, J. B., Cheney, J., Cooper, P. J., Grimwood, K., Robertson, C. F., Tiddens, H. A., Wainwright, C. E., Australasian Cystic Fibrosis Bronchoalveolar Lavage Study, Investigators, Costs of bronchoalveolar lavage-directed therapy in the first 5 years of life for children with cystic fibrosis, Journal of	**Study dates** 1999 to 2009 **Intervention** Bronchoalveolar Lavage BAL) directed therapy: underwent BAL at enrolment with hospitalisation for IV antibiotics to treat exacerbations if *P.aeruginosa* was cultured from OP specimens after *P.aeruginosa* eradication therapy **Comparison(s)** Standard therapy: diagnosis was dependent upon	**Source of effectiveness data** Study participants included the RCT by Wainwright 2011 **Source of cost data** Country specific unit costs: • BAL according to length of stay using one of the DRG code specific to bronchoscopy • Drug costs in Australia from the Pharmaceutical Benefits Schedule (PBS), NZ from the Pharmaceutical Management Agency of NZ (PHARMAC), or MIMS • Professional attendances costed on	**Time horizon and discount rate** • Time horizon: 5 years • Discount rate: NA **Method of eliciting health valuations (if applicable)** NA **Modelling approach** NA	**Cost per patient per alternative** Mean±SD BAL therapy; standard therapy; MD (95%CI) • Total pathology: 828±342; 847±414; -19 (-140 to 101) • Total procedures: 12,328±8,540; 1,046±1,944; 11,283 (9,335 to 13,231) • Total professional attendances: 12,326±3,053; 11,943±3,233; 384 (-608 to 1,375) • Total phamaceuticals: 9,415±8,799; 9,895±10,890; -481 (-3,611 to 2,649) • Total: 92,860±73,378; 90,958±110,255; 1,902 (-27,782 to 31,586) Disaggregated costs also reported in the study **Effectiveness per patient per alternative** Not reported	**Limitations** Adverse events and quality of life not reported which may overestimate benefits and cost-effectiveness of BAL compared to standard therapy **Other information**

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Pediatrics, 165, 564-569.e5, 2014 **Ref Id** 363207 **Economic study type** Cost- benefit analysis **Country(ies) where the study was done** Australia and New Zealand **Perspective & Cost Year** Perspective: healthcare provider Cost year: 2010 **Source of funding** Supported by the Austalian National Health and Medical Research Council and the	OP cultures and treatment was often empiric	hourly rates in the Victorian Ambulatory Classification and Funding system • Test using the Medical Benefits schedule for Australia and Monosty of Health for NZ • During the study tobramycin solution for inhalation was not licensed in Australia or NZ and was provided free to study participants by the manufacturer, but the 2011 PBS dispensed price (AUD 2137.76 for 56 ampoules of 300mg/5ml) was used Cost categorised into: • Pharmaceuticals taken at home or hospital and vitamin supplements • Pathology into OP swab culures, nasopharyangeal aspirate. serum urea and electrolytes, liver function tests, full blood count, fecal fat • Procedures into chest radiographs, BAL, audiology		**Incremental cost-effectiveness** Not reported **Other reporting of results** NA **Uncertainty** SD and 95% confidence intervals presented	

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Children's Hospital Foundation Queensland. Tobramycin inhalation solution and delivery system used throughout the study supplied by Pathogenesis		• Professional attendances into baseline assessment, annual review, routine clinic visit, exacerbations, review of treatment, physiotherapy **Other data sources e.g. transition probabilities** NA			
Full citation McIntyre, A. M., Dornase alpha and survival of patients with cystic fibrosis, Hospital Medicine (London), 60, 736-9, 1999 **Ref Id** 363308 **Economic study type** Cost-effectiveness analysis.	**Study dates** NA, model assumptions based on the findings from several clinical trials (note published on or before 1997). **Intervention** Dornase alpha at different FEV improvements (8%, 4.3%, 20%) **Comparison(s)** Dornase alpha at different FEV	**Source of effectiveness data** <u>Anticipated cost saving from improved clinical outcomes</u> Cost savings from RTI-related care would offset between 18.3% and 37.5% of the acquisition cost of dornase alpha based on Oster et al. 1995 <u>Improved clinical outcomes</u> Evidence on the mean days in hospital, days on parenteral antibiotics and days at home as a result of CF-related illness over a 24 week period were taken from Fuch et al. 1994 and Oster et al. 1995 and multiplied to provide an annual estimate	**Time horizon and discount rate** • Time horizon: lifetime (up to the age of 41 in the base case) • Discount rate: 6% **Method of eliciting health valuations (if applicable)** NA **Modelling approach** Attempts to model the delayed progression	**Cost per patient per alternative** Offsetting the cost of dornase alfa (£7,200 per annum) by 18.3%, the discounted lifetime cost for the CF patient would be £233,070 including the acquisition cost of dornase alpha and the additional cost of treatment for 3 extra years of life. <u>Improvement with dornase alpha: 8%; 4.3%; 20%</u> • Lifetime costs, 18.3% offset: £151,264 (no dornase alpha); £233,070; £241,731; £223,440 • Lifetime costs, 37.5% offset: £212,218; £221,093; £201,845 • Additional cost of dornase alpha per year, 18.3% offset: £2,479; £2,827; £1,951 • Additional cost of dornase alpha per year, 37.5% offset: £1,847; £2,182; £1,367 **Effectiveness per patient per alternative**	**Limitations** • Assumed that once FEV dropped below 28% death would occur, whereas in clinical practice today these patients may undergo the cost of a lung-transplant which would increase their length and quality of life • Assumptions for disease progression and survival may reflect outdated practices and underestimate their effects in

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Country(ies) where the study was done UK, note clinical effectiveness data taken from US clinical trials **Perspective & Cost Year** Not reported, but cost of CF treatment taken directly from Robson et al. 1992. **Source of funding** Not reported.	improvements (8%, 4.3%, 20%) or no dornase alpha	<u>Disease progression and survival, assumptions used in the model</u> • Konstan et al. 1995, before the age of 13 years, lung function declined at a rate of 4.2% per annum and from the age of 13 years by 2.77% • Shah et al. 1995, mean sustained improvement in FEV over 18 months with once daily dornase alpha of 8% • Starting point for prescribing dornase alpha was assumed to be FEV 70% of predicted, approximately 8 years of age • Provided a response is noted the patient will be maintained on dornase alpha until death • Kerem et al 1992, patients with FEV<30% had a 50% chance of dying within 2 years - for the model simplified to assume once FEV dropped below 28% death would occur • 3 additional years of life would be gained by the	of lung function and the possible increased survival time of a patient who positively responds to dornase alpha.	<u>Improvement with dornase alpha: 8%; 4.3%; 20%</u> • Age at death: 38 (no dornase alpha); 41; 40; 45 • Life years gained: 3; 2; 7 • Difference in days in hospital: -65; -76; -20 • Difference in days on parenteral antibiotics: -154; -171; -86 • Difference in days at home as a result of CF-related illness: -94; -101; -68 **Incremental cost-effectiveness** Not reported **Cost per life year gained (not incremental)** <u>Improvement with dornase alpha: 8%; 4.3%; 20%</u> • 18.3% offset: £27,269; £45,234; £10,311 • 37.5% offset: £20,318; £34,915; £7,226 **Uncertainty** • Improvements with dornase alpha varied using 4.3% (taken from the product monograph), 8% (Shah et al. 1995) and 20% (Davies et al. 1997) • Cost offsets varied using 18.3% and 37.5% • An increase in the cost of annual care for CF severe patients (FEV<40%) of £30,000 (Fogarty 1996) - this scenario reduced the cost per life year gained to a range of £45,173 (4.3% improvement, 18.3% offset) to £6,084 (20% improvement, 37.5% offset)	clinical practice today • NICE reference case specifies a discount rate of 3.5% rather than 6% used in the model - a higher rate will underestimate the costs • Unable to verify how Robson et al. 1992 costed CF care • Unable to verify patient characteristics included in the trials used to inform assumptions on disease progression and survival • Cost year unclear and costs are not reported to be inflated to the same year **Other information**

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
		patient on dornase alpha (age at death 41 years with dornase alpha vs. 38 years without) **Source of cost data** • Based on costing data reported by Robson et al. 1992 assumed that the annual cost of treatment for a mild CF patient would be £2,792, for moderate £8,241 and for severe £19,995 • All future costs were discounted at 6%, the discounted lifetime cost for a CF patient was estimated to be approx. £151,264 • Cost savings from RTI-related care would offset between 18.3% and 37.5% of the acquisition cost of dornase alpha based on Oster et al. 1995 **Other data sources e.g. transition probabilities** NA			

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Full citation Iles, R., Legh-Smith, J., Drummond, M., Prevost, A., Vowler, S., Economic evaluation of Tobramycin nebuliser solution in cystic fibrosis, Journal of Cystic Fibrosis, 2, 120-8, 2003 **Ref Id** 331135 **Economic study type** Cost consequence analysis **Country(ies) where the study was done** 8 UK centres recruited a total of 71 patients **Perspective &**	**Study dates** Not reported, but 12 months of data before and during the use of TNS were obtained. **Intervention** • 300mg tobramycin in 5ml nebulised twice daily for 28 days (TNS) • After 28 days of therapy subjects stopped therapy for the next 28 days **Comparison(s)** Usual therapy without TNS.	**Source of effectiveness data** • Effectiveness (FEV1 % predicted, number of days in hospital, outpatient visits, ICU admissions, ward admissions, use of intravenous antibiotics) estimated from a matched case-control study including 41 TNS treated patents and 30 matched controls from the same clinic • The main analysis was of the larger group of 41 TNS treated patients because of evidence of imbalance between the TNS and matched control groups **Source of cost data** • Unit costs of ward and ICU stays were taken from the NHS and Trust Finance Returns 2001 • Drug cost sources are not reported **Other data sources e.g.**	**Time horizon and discount rate** • Time horizon: 12 months • Discount rate: NA **Method of eliciting health valuations (if applicable)** NA **Modelling approach** NA	**Cost per patient per alternative** <u>Estimated from 41 patients who received TNS, comparing 12 months before and 12 months during the use of TNS.</u> Pre mean; post mean; **mean change post-pre** (95% CI) • FEV1% predicted: 56.2; 54.9; -1.26 (-3.34 to +0.83) • Days in hospital: 32.0; 24.2; -7.8 (-13.0 to -3.2) • Length IVs, days: 55.4; 38.9; -16.4 (-27.4 to -7.9) • IV courses: 3.6; 2.6; -0.98 (-1.71 to -0.45) • Ward admissions: 3.0; 2.2; -0.83 (-1.52 to -0.32) • ICU admissions: 0.1; 0.2; **+0.05** (-0.20 to +0.59) **Effectiveness per patient per alternative** Estimated from 41 patients who received TNS, comparing 12 months before and 12 months during the use of TNS. Pre mean; post mean; **mean change post-pre** (95% CI) <u>Cost components</u> • Tobramycin nebulised solution: 0; £10,010; +£10,010 (+£10,010 to +£10,010) • Hospitalisation: £10,897; £8,552; -£2,345 (-£4,932 to £120) • Drug: £11,205; £9,832; **-£1,374** (-£3,184 to -£33) <u>Drug cost components</u> • Antibiotics: £6,716; £5,373; **-£1,**344 (-£3,296 to -£97)	**Limitations** • The observational design and imbalance between the TNS and matched control groups questions if the results are generalisable • Other interventions and medications taken on and off study treatment were recorded and costed, but none of those drugs were explicitly stopped during the study period • Sources for cost components and drug costs not reported • Absence of detail regarding cost build up for: TNS costs, drug costs, ward costs and ICU costs • It is unclear how the number of days in hospital has been disaggregated into ward costs and

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Cost Year • Cost year 2001 • NHS non-societal perspective **Source of funding** Sponsored and financially supported by Chiron Ltd.		**transition probabilities** NA		• Other drug: £4,489; £4,459; -£3**0** (-£185 to +£124) <u>Hospitalisation costs</u> • Ward: £9,715; £7,246; **-£2,469** (-£4,564 to -£914) • ICU: £1,182; £1,306; +£124 (-£2,052 to +£4,634) <u>Total cost</u> • £22,102; £28,394; **+£6,292** (+£3,138 to +£9,193) **Incremental cost-effectiveness** NA **Other reporting of results** • In the 41 patients treated with TNS the total acquisition cost of TNS (£10,010) may be reduced by the cost savings of £2,245 from hospitalisation and £1,374 from drugs, giving a net cost of £6,292 per annum • Therefore the TT notes that the additional cost of TNS was not completely offset by reductions in other mean health care expenditure because the net cost is positive **Uncertainty** Not assessed, but 95% CIs are reported for clinical and cost outcomes.	ICU costs • The authors state that the mean costs of hospitalisation (£313.15 per day) and ICU admissions (£1,275 per day) were based on general and medical paediatric and adult beds which may underestimate ward care costs in CF **Other information** Chronic infection was defined as the presence of *P.aeruginosa* in a sputum/throat culture on two occasions over six months during the year prior to and on one occasion following the start of TNS.

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Full citation Suri, R., Grieve, R., Normand, C., Metcalfe, C., Thompson, S., Wallis, C., Bush, A., Effects of hypertonic saline, alternate day and daily rhDNase on healthcare use, costs and outcomes in children with cystic fibrosis, Thorax, 57, 841-6, 2002 **Ref Id** 360305 **Economic study type** Cost-consequence analysis **Country(ies) where the study was done** UK	**Study dates** Not reported. **Intervention** Daily 2.5mg rhDNase. Alternate day 2.5mg rhDNase. **Comparison(s)** 5ml 7% hypertonic saline (HS)	**Source of effectiveness data** A prospective, open, randomised, crossover trial in completed by 43 children aged 5 to 18 years, this trial included a 2 week wash-out period. <u>Patient characteristics</u> • Age, mean years 12.6 (SD 2.8) • FEV1, mean 48% (SD 15) • FVC, mean 68% (SD 22) • Females, n=28 (60%) • *P.aeruginosa*, n=17 (36%) • *S.aureus,* n=13 (28%) • Both *P.aeruginosa* and *S.aureus*, n=5 (11%) • HS treatment at enrolment, n=2 (4%) • rhDNase treatment at enrolment, n=39 (83%) **Source of cost data** • Hospital contacts (inpatient, outpatient, day case) radiological	**Time horizon and discount rate** • Time horizon: 12 weeks • Discount rate: NA **Method of eliciting health valuations (if applicable)** NA **Modelling approach** NA	**Cost per patient per alternative** <u>Daily rhDNase (n=40) vs. HS (n=40)</u> <u>Mean costs over 12 weeks</u> *Intervention:* £1,755 vs. £37 *Non-intervention drugs* • IV antibiotics: £601 vs. £748 • Oral antibiotics: £95 vs. £112 • Other drugs: £1,575 vs. £1,503 • Subtotal: £2,271 vs. £2,361 *Hospital care* • Inpatient: £1,483 vs. £1,669 • Outpatient: £49 vs. £48 • Ward review: £56 vs. £89 • Investigations: £26 vs. £29 • Procedures: £30 vs. £18 • Subtotal: £1,643 vs. £1,855 *Community care* • GP contacts: £7 vs. £18 • Other contacts: £18 vs. £22 • Subtotal: £25 vs. £28 **Grand total: £5,694 vs. £4,285** **MD (95% CI): £1,409 (£440 to £2,318)** <u>Daily rhDNase (n=43) vs. alternate day rhDNase (n=43),</u>	**Limitations** • 83% of patients were already receiving rhDNase at enrolment - these patients may increase the effectiveness of rhDNase if they are known to respond positively to rhDNase, or if rhDNase gets less effective over time this could reduce the effectiveness of rhDNase as the mahotiry of participants are not naïve patients. • The cost of nebulisers do not appear to be included in the cost of treatment, but from the % of patients receiving rhDNase or HS at enrolment, participants would already own one. **Other information**

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Perspective & Cost Year Cost year 1999/2000. NHS non-societal perspective. **Source of funding** NHS Health Technology Assessment Programme.		investigations, blood tests, drugs, and the use of community services (including community nurse, physiotherapist, and general practitioner) were recorded for each patient. • Unit costs of health services were collected at the 2 hospitals where patients were recruited from and a local DGH, drug costs were taken from the BNF, and community care costs from Netten et al. 1999. • Unit cost of rhDNase £20.39 per day; HS, £0.38 per day • For each treatment comparison, the incremental cost was calculated as the difference in total costs and refers to a 12-week period. **Other data sources e.g. transition probabilities** NA		<u>mean costs over 12 weeks</u> *Intervention*: £1,749 vs. £857 *Non-intervention drugs* • IV antibiotics: £679 vs. £702 • Oral antibiotics: £101 vs. £110 • Other drugs: £1,587 vs. £1,537 • Subtotal: £2,367 vs. £2,349 *Hospital care* • Inpatient: £1,404 vs. £1,769 • Outpatient: £60 vs. £53 • Ward review: £50 vs. £46 • Investigations: £28 vs. £50 • Procedures: £29 vs. £49 • Subtotal: £1,571 vs. £1,968 *Community care* • GP contacts: £7 vs. £5 • Other contacts: £17 vs. £19 • Subtotal: £24 vs. £24 **Grand total: £5,711 vs. £5,198** **MD (95% CI): £513 (-£546 to £1,510)** <u>Daily rhDNase vs. HS, MD (95% CI)</u> *Hospital resource use*	Mean unit costs from the DGH are a lot cheaper than the two postgraduate centres, for total inpatient care there is a difference of £397.33 vs. £280.22, for total outpatient clinics £84.31 vs. £51.24, and for total ward reviews £148.28 vs. £67.17, this is largely due to overhead costs and capital costs. rhDNase and HS were administered using a Durable Sidestream nebuliser and Porta-Neb compressor. HS was inhaled twice daily immediately before the patients regular physiotherapy. rhDNase was administered once a day or once every other day, at least 1 hour before physiotherapy.

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
				• Hospital admissions: 0.63 vs. 0.53, 0.10 (-0.15 to 0.35) • Inpatient days: 4.73 vs. 5.13, -0.40 (-2.32 to 1.52) • Due to pulmonary exacerbations: 2.33 vs. 4.28, -1.95 (-4.22 to 0.32) • Outpatient visits: 0.93 vs. 1.23, -0.30 (-0.71 to 0.11) • Day case visits: 0.33 vs. 0.35, -0.03 (-0.30 to 0.25) • Days of IV antibiotic therapy: 9.45 vs. 10.38, -0.93 (-4.45 to 2.60) *Community service use* • GP contacts: 0.30 vs. 0.25, 0.05 (-0.17 to 0.27) • Nurse contacts: 1.75 vs. 2.70, -0.95 (-0.17 to 0.25) • Physiotherapist contacts: 0.33 vs. 0.10, 0.23 (-0.09 to 0.54) <u>Daily rhDNase vs. alternate ay rhDNase, MD (95% CI)</u> *Hospital resource use* • Hospital admissions: 0.63 vs. 0.79, -0.16 (-0.41 to 0.09) • Inpatient days: 4.47 vs. 5.40, -0.93 (-3.24 to 1.38) • Due to pulmonary exacerbations: 2.21 vs. 2.91, -0.70 (-2.74 to 1.34) • Outpatient visits: 1.00 vs. 0.86, 0.14 (-0.28 to 0.56) • Day case visits: 0.37 vs. 0.40, -0.02 (-0.31 to 0.27) • Days of IV antibiotic therapy: 9.56 vs. 8.84, 0.72 (-2.36 to 3.81) *Community service use*	

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
				• GP contacts: 0.28 vs. 0.21, 0.07 (-0.14 to 0.28) • Nurse contacts: 1.70 vs. 2.26, -0.56 (-3.43 to 2.32) • Physiotherapist contacts: 0.30 vs. 0.12, 0.19 (-0.02 to 0.39) **Effectiveness per patient per alternative** <u>Mean FEV increase at 12 weeks from baseline</u> • Daily rhDNase 16 (25)% • Alternate day rhDNase 14 (23)% • HS 3(21)% **Incremental cost-effectiveness** NA **Other reporting of results** • Reducing the rhDNase costd by 10% and 30%, the mean additional costs of rhDNase compared with HS fell to £1234 and £884, and the mean additional costs of daily compared with alternate day rhDNase were £42 and £246. • The results were insensitive to changes in the cost per bed day. **Uncertainty**	

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
				• Mean incremental costs and benefits was reported with 95% CIs calculated using nonparametric bootstrap methods. • Scenarios reducing the price of rhNDase reported by the BNF by 10-30% and 20th and 80th percentiles of the costs per occupied bed day.	
Full citation Wolter, J. M., Bowler, S. D., Nolan, P. J., McCormack, J. G., Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and cost aspects, European Respiratory Journal, 10, 896-900, 1997 **Ref Id** 363511 **Economic study type**	**Study dates** Not reported **Intervention** Home IV antibiotic therapy following a respiratory exacerbation **Comparison(s)** Hospital IV antibiotic therapy following a respiratory exacerbation	**Source of effectiveness data** • Prospective, randomised trial. • Mean age 22 years (range 19 to 41). • 17 patients enrolled had 31 admissions (hospital n=18, home n=13). **Source of cost data** • Hospital costs from inpatient stays were valued in Australian dollars (A$) at 1992–3 prices, calculated using CF inpatient costs from the Prince Charles Hospital and from projected diagnostic-related group (DRG) reimbursement figures.	**Time horizon and discount rate** • Time horizon: unclear, post-Rx defined as 10 days after cessation of IV therapy • Discount rate: NA **Method of eliciting health valuations (if applicable)** The Chronic Respiratory Disease Questionnaire (CRDQ) was administered on Day 0 and post-Rx to produce a score (not a utility value).	**Cost per patient per alternative** • Home therapy (mean A$15.08, SD A$13.48 per day) was cheaper for families than hospitalisation (mean A$23.77, SD A$17.77 per day of hospitalisation) • The estimated cost saving for managing exacerbations at home compared with hospital was estimated to be A$2552 - this figure includes costs of home physiotherapy, home visits, training, equipment, drugs and bed occupancy. **Effectiveness per patient per alternative** No significant difference reported for the clinical outcomes: • weight (p=0.10) • 12 min walk (p=0.11) • sputum weight g (p=0.09) • oximetry % (p=0.44) • FEV1% (p=0.27) • FVC% (p=0.30)	**Limitations** • Unclear if all costs have been inflated to the same year • Small sample size - 17 out of 54 were considered eligible to include in the trial • The number of patients in each arm is not reported - instead the authors report the number of admissions per arm • Old study conducted in Australia that may not reflect UK clinical practice today

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Cost-consequence analysis **Country(ies) where the study was done** Australia **Perspective & Cost Year** Perspective not clearly stated as the authors appear to include costs incurred by the hospital and by patients and families. Cost year 1992/3 (defined for hospital costs). **Source of funding** Not reported		• Home therapy costs were calculated based on hospital acquisition costs and consumption of resource • Staff costs spent on education and home visits were calculated from hourly wages • Travel costs were determined according to a standard cents-per-kilometre fee • Other patient and family costs were determined by interview **Other data sources e.g. transition probabilities** NA	**Modelling approach** NA	QoL outcomes: • hospital patients fared better in terms of fatigue, mastery and total score ($p<0.05$) • home patients fared better in terms of personal, sleep and total disruption ($p\leq0.005$) **Incremental cost-effectiveness** NA **Other reporting of results** **Uncertainty** Not assessed.	**Other information** • All patients had colonisation of *P.aeruginosa* • Antibiotic treatment consisted of ceftazidime 2g, 12-hourly, and tobramycin 4–6 mg/kg daily as a single bolus - treatment was conducted for a minimum of 10 days and was guided by clinical response • Patients also received twice-daily physiotherapy plus 20 minutes of aerobic exercise • Patients randomised to home therapy spent 2-4 days in hospital before discharge and were taught to prepare and administer their own IV antibiotics.

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Full citation Health Technology Assessment, Mannitol dry powder for inhalation for the treatment of cystic fibrosis, Health Technology Assessment Database, 2015 **Ref Id** 360457 **Economic study type** Cost-utility analysis **Country(ies) where the study was done** Economic evaluation undertaken in the UK. Clinical effectiveness data obtained from 2 multicentre trials undertaken	**Study dates** **Intervention** Mannitol dry powder, 400mg bd **Comparison(s)** • rhDNase users: for those patients currently on rhDNase, the comparison will be: rhDNase + BSC vs. rhDNase + Bronchitol + BSC • rhDNase non-users: for patients who are ineligible, intolerant or inadequately responsive to rhDNase, the appropriate comparison will be Bronchitol + BSC vs. BSC	**Source of effectiveness data** Two double blind randomised controlled studies with a 26 week (blinded phase) and 26 weeks(open label phase) Patient characteristic for adult patients only. *1. DPM-CF-301 - bronchitol 400mg bd (n=177) vs. bronchitol 50mg bd (control, n=118)* • Mean age 29.3 years • 44.2% female • 97.9% Caucasian • Baseline FEV predicted 57.8% • rhDNase use 53.7% *2. DPM-CF302 - bronchitol 400mg bd (n=184) vs. bronchitol 50mg bd (control, n=121)* • Age range 18 to 53, mean NR • 39.1% female • 99.3% Caucasian • Baseline FEV predicted 61.1%	**Time horizon and discount rate** Time horizon: lifetime Discount rate: 3.5% First cycle 6 weeks, second cycle 8 weeks, subsequent cycles 12 weeks **Method of eliciting health valuations (if applicable)** Health related quality of life was assessed via the Health Utility Index (HUI) in the pivotal clinical trials of Bronchitol collected at visit 0 (screening), visit 3 (week 12), visit 4 (week 26) and at termination in case of early withdrawal. A HUI2 global utility score was determined for each patient according to the HUI Procedures Manual. The following utility values were estimated to inform the model: • Baseline utility 0.899	**Cost per patient per alternative** Results are based on 100,000 simulations • Control (baseline) £180,188 • Bronchitol £211,923 • Control + rhDNase £249,472 • Bronchitol + rhDNase £285,858 **Effectiveness per patient per alternative** Results are based on 100,000 simulations Life years gained; QALYs • Control (baseline): 11.40; 9.75 • Bronchitol: 12.10; 10.52 • Control + rhDNase: 11.40; 9.75 • Bronchitol + rhDNase: 12.10; 10.52 **Incremental cost-effectiveness** Results are based on 100,000 simulations • Mannitol vs. control, ICER £41,074 • Mannitol + rhDNase vs. control + rhDNase, ICER £47,095 **Other reporting of results** The probability of the ICER being below a WTP threshold of £30,000 was 25.8% for Bronchitol mono-therapy and	**Limitations** The Assessment Group stated the following: • Costs and utilities were assumed to be treatment specific in the manufacturer's submission. The preferred approach is to define costs and utilities that are health state specific, so that when treatment influences number of patients per health state and the time spent in these states indirectly costs and effects are influenced • The technologies were not appropriately defined to match the scope in terms of rhDNAse use. Data from all adult patients were used to inform both the cost-effectiveness of mannitol versus

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
in 11 countries. **Perspective & Cost Year** UK NHS non-sociatel perspective. Cost year 2009. **Source of funding** NA: HTA		• rhDNase use 69.5% In line with the expected licensed indication only the adult patients (aged 18 or above) from these two trials have been included **Source of cost data** • Resources were costed at patient level. • Prices were taken from National reference costs 2008/2009, BNF 59, and PSSRU 2009. • Resources were recorded in both pivotal studies from medical records, discharge summaries and patient's diaries: • Total 6-monthly cost CF patient treated with Bronchitol £4,391 • Total 6-monthly cost CF patient treated with Control £4,664 • The cost of a pulmonary exacerbation (£6,115) was calculated by taking the mean overall cost for patients experiencing 1 PDPE and subtracting the	• Change in utility from baseline for patients treated with Bronchitol with improvement in respiratory symptoms 0.019 • Change in utility from baseline for patients treated with BSC with improvement in respiratory symptoms 0.009 • Change in utility from baseline for patients treated with Bronchitol without improvement in respiratory symptoms -0.022 • Change in utility from baseline for patients treated with BSC without improvement in respiratory symptoms -0.046 • Utility patient with improvement in respiratory symptoms 0.918 • Utility improvement in	16.4% for Bronchitol add-on therapy. At a WTP threshold of £20,000 these probability were 10.9% and 7.4%, respectively. The key drivers of the model are: • The cost of Bronchitol and the RR of pulmonary exacerbations in the Bronchitol arm. This is because an exacerbation has an impact on both costs and QALY's • The impact of pulmonary exacerbations on a patient's QoL • The patient's FEV1 % predicted when initiating Bronchitol treatment • The improvement in FEV1 % predicted caused by Bronchitol • The hazard rate of FEV1 % predicted • Utility for patients without improvement in respiratory symptoms **Uncertainty** • Deterministic sensitivity analysis was undertaken using minimum and maximum values for a large number of model inputs • The model was run with 100,000 iterations each run and the most sensitive parameters are displayed in a tornado diagram • The time horizon (1, 5, 10 and 20 years) and CF mortality (increased by 20% and 50%) was varied • Probabilistic sensitivity analysis was undertaken and presented on a cost-effectiveness plane and CEAC • Several scenario analyses have been performed on the relative risk of pulmonary exacerbation and discontinuation rule, decline in	control and of mannitol plus BSC versus BSC. Also, in the incremental analysis, mannitol plus rhDNAse was treated as if it could be prescribed to the same population as mannitol alone • There is uncertainty in the duration of effectiveness of mannitol treatment. If mannitol would lose effectiveness after 5 years, the ICER will increase dramatically from the base case • The disutility value due to exacerbation used in the model was based on the utility of a severe exacerbation, but throughout the model description, it is not clear which type of exacerbations are considered • The rate ratio presented does

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
		mean cost for all patients not having a PDPE during the 26-week time period • The cost of a lung transplant (£35,458) was taken from NHS Reference Costs (elective inpatient, DZ01Z) • The follow-up cost after a lung transplant (£87,431) was taken from a UK study (Anyanwu et al. 2001) which reported the mean cost up to 15 years after lung transplant in 1999 UK pounds sterling at an annual discount rate of 6% - this total mean cost was adjusted to 2009 price level and corrected to the 3.5% inflation rate **Other data sources e.g. transition probabilities** <u>Effect on lung function estimated from CF-301 and CF-302</u> • A linear regression analysis was performed	respiratory symptoms control 0.908 • Utility no improvement in respiratory symptoms 0.877 • Utility no improvement in respiratory symptoms control arm 0.853 <u>Utility values obtained from the literature:</u> • Utility decrement for exacerbation, -0.23 taken from Bradley et al. 2010 who administered the EQ-5D in 94 patients in the UK • Assumed that the duration of the detrimental effect on a patient's QoL corresponded to the overall median days (14; range 1-361) on IV antibiotics in hospital as	lung function and pulmonary exacerbation rate	not distinguish between patients receiving mannitol as add-on therapy and those receiving mannitol as second line therapy. Thus, the ERG requested information on the effect of treatment on the exacerbation rate for rhDNase users (add-on treatment) and rhDNase non-user unsuitable (second line treatment). • An implicit assumption is made that best supportive care is equal to best supportive care + rhDNase in terms of effectiveness **Other information** <u>Pulmonary exacerbation rates</u> • Due to the lack of information on exacerbations in

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
		to obtain a prediction of the FEV1 % predicted at the end of the trial follow-up period, i.e. week 26 • Variables in the model include treatment group (1.52), BMI at baseline (0.37), FEV% predicted at baseline (0.93), PDPE during DBP (-2.16) and responder (6.63) • Assume that the benefit in lung function achieved in the first six months will be maintained over the patient's lifetime, assuming that he/she will receive therapy for the remainder of his life <u>Pulmonary exacerbations estimated from CF-301 and CF-302</u> The relative risk of having a PDPE for patients who respond to Bronchitol was calculated by the observed difference in PDPE rate in patients who responded to Bronchitol compared to the overall PDPE rate in the Control group: • Relative risk	reported in the UK CF registry report • Utility for patients with FEV<30, 0.31 and utility for lung transplant patients, 0.80, taken from Anyanwu 2001 who used the EuroQoL to assess QoL in UK patients before (n=87) and after (n=255) lung transplantation **Modelling approach** <u>Patient-level simulation Markov model</u> The model includes the following health states: • Cystic fibrosis • Improved respiratory symptoms • Lung transplant • Death due to CF • Death due to		the BioGrid database, the number of inpatient hospital admissions per quarter was used as a proxy for the rate of exacerbations • The pulmonary exacerbation rate used in the model was the rate observed in adults under the age of 30 years (0.700 per year) • For patients aged 30 or above this was corrected by applying a relative risk of 1.38 (0.969/0.700) to the baseline risk • The exacerbation rate in patients on Bronchitol treatment was reduced by the RR observed in the pooled DMP-CF-301 and DMP-CF-302 adult population (RR = 0.66) • Finally the exacerbation rate was increased for

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
		exacerbation with Bronchitol (patients who respond to treatment) 0.66 • RR for patient experiencing an exacerbation over the age of 30 1.38 • RR of experiencing an exacerbation if patient has experienced an exacerbation in the previous year 1.59 • Annual exacerbation rate control group 0.70 based on BioGrid data <u>Respiratory symptoms estimated from CF-301 and CF-302</u> • Probability of improved respiratory symptoms at week 14 (V3) for pts treated with Control 0.458 • Probability of improved respiratory symptoms at week 26 (V4) for Control pts 0.154 • Probability of continuing to have improved respiratory symptoms at week 26 (V4) for pts treated with Control 0.745	unrelated cause As patients move through the model one at a time, the model memorises specific patient characteristics includi ng FEV, age, history of exacerbations and BMI to determine their transition probabilities through the tree: • All patients start in 'Cystic Fibrosis' and based on their lung function measured by FEV1 they either continue treatment (FEV1 ≥30%), or they are eligible for a lung transplant (FEV1 <30%) • Patients not responding to Bronchitol treatment will stop Bronchitol treatment and switch to standard therapy		patients who experienced a pulmonary exacerbation in the previous 48 weeks by applying a relative risk of 1.59 <u>Decline in lung function over time</u> • Estimated from a fixed model analysis from BioGrid Data • The model shows that lung function decreases on average by 1.02% per year to the age of 30 after which it tends to increase slightly by 0.64% per year • Hospitalisation (exacerbation) during the previous 3 months is associated with a 2.08% decrease in lung function <u>Lung transplant mortality</u> Mortality for patients who received a lung

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
		• Probability of improved respiratory symptoms at week 14 (V3) for pts treated with Bronchitol 0.394 • Probability of improved respiratory symptoms at week 26 (V4) for Bronchitol pts 0.165 • Probability of continuing to have improved respiratory symptoms at week 26 (V4) for pts treated with Bronchitol 0.687 <u>Transition probability to "Lung Transplant"</u> • Based on the UK CF Registry Annual Data Report 2008. Of those with complete data in 2008, 126 patients had been evaluated and 55 accepted onto the transplant list. 24 received transplants (probability 0.19)	(the control arm) • The rate of pulmonary exacerbations depends upon the patient's age, the history of exacerbations in the previous year and whether the patient is receiving Bronchitol or standard therapy • In addition the patient may experience improvement in respiratory symptoms, which corresponds to a slightly improved quality of life • Each cycle the patient has the chance to die due to CF or to unrelated cause • By default the probability of dying is based on the lung function and age; however this probability is elevated when the patient has an exacerbation		transplant were based 10-year survival data from UK patients receiving a lung transplant between 1995-1997 <u>CF mortality</u> • A Cox's proportional hazard survival model for CF survival from birth to CF-related death was developed from BioGrid data • FEV1 % predicted and BMI were included as time varying covariates • Relative risk of death due to a Bcc infection in combination with an exacerbation is 3.41

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
			in combination with a Bcc infection • For the first 26 weeks of the economic model for adults an analysis of individual patient level data is undertaken for all adult patients treated with Bronchitol. From here the model extrapolates to a lifetime horizon based on observational data from an Australian database (BioGrid), supplemented with literature data <u>Continuation rule</u> • A responder to treatment is defined as a relative increase of at least 5% or an absolute increase of at least 100ml in		

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
			the FEV1 at week 6 from baseline • Patients on Bronchitol who are responders according to the above definition, will continue treatment for the rest of their life • Patients on Bronchitol who are non-responders, will discontinue the treatment with Bronchitol and be switched to a best supportive care which is identical to the Control arm		
Full citation Menzin, J., Oster, G., Davies, L., Drummond, M. F., Greiner, W., Lucioni, C., Merot, J. L., Rossi, F., vd Schulenburg, J. G., Souetre, E., A multinational economic	**Study dates** Analyses undertaken between 1992-3 **Intervention** 2.5 mg daily rhDNase	**Source of effectiveness data** • Phase III double-blind, multicentre, clinical trial undertaken in the US by Oster et al. 1995 • The reduction in risk of RTI among patients who received rhDNase in the US trial was believed to be generaliable to other settings: discussions	**Time horizon and discount rate** • Time horizon: 24 weeks • Discount rate: NA **Method of eliciting health valuations (if**	**Cost per patient per alternative** Only report the difference in the mean costs between placebo and rhDNase **Effectiveness per patient per alternative** <u>Mean health care utilisation over 24 weeks for patients in the US trial</u> Placebo (n=325); 2.5mg daily rhDNase (n=322) RTI related reasons	**Limitations** • Practice-adjustment analyses were only undertaken for Italy and France in the likelihood of hospitalisation for a RTI as these patients were believed to be

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
evaluation of rhDNase in the treatment of cystic fibrosis, International Journal of Technology Assessment in Health Care, 12, 52-61, 1996 **Ref Id** 360478 **Economic study type** Cost-benefit analysis **Country(ies) where the study was done** UK, note estimated healthcare utilisation and costs among CF patients in France, Germany, Italy and the UK, only UK estimates are reported here. **Perspective &**	**Comparison(s)** Placebo	with CF experts in the UK indicated that the frequency of hospitalisation was comparable to the US trial (approx. 80%) and the mean length of hospitalisation was approx. 12 days. These difference were not believed to be large enough to warrant adjustment, **Source of cost data** • Measures of physical resource use were compared between patients who received rhDNase vs. placebo in the US trial (Oster et al. 1995) • Hospitalisations were designated as RTI-related if an antibiotic was given parenterally and the investigator indicated that the reason for therapy was "treatment of respiratory tract infections" • Differences in RTI-related resource use were then evaluated using local (country	**applicable)** NA **Modelling approach** NA	• Hospital admission: 0.56; 0.41 • Inpatient days: 6.4; 4.9 • Days of inpatient IV antibiotic therapy: 6.2; 4.8 • Days of inpatient oral antibiotic therapy: 0.55; 0.59 • Days of outpatient IV antibiotic therapy: 4.4; 2.9 • Days of outpatient oral antibiotic therapy: 25.2; 23.5 **Incremental cost-effectiveness** <u>Difference in the mean costs of RTI-related care (placebo - rhDNase) over 24 weeks</u> • Inpatient care, days in hospital £300 • Inpatient care, antibiotic therapy £50 • Outpatient care £84 • Total £434 **Other reporting of results** Using the lower costs of inpatient treatment savings are £300 **Uncertainty** Used alternative estimates of the daily costs of inpatient treatment, in the UK the lowest (£145) and highest (£347) estimates from 3 CF centres were used	treated as outpatients rather than inpatients - the authors do not justify if this difference applies to the UK • The cost of rhDNase therapy was not included, as it was not being marketed at the time the assessment was undertaken, therefore we cannot known of the cost of treatment is offset by cost savings from improved clinical outcomes • The authors note that not all relevant costs of RTI-related care were captured , for example, patients may require additional physician visits as well as respiratory therapy which were not documented in the US trial • Little detail regarding sources

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Cost Year UK NHS non-societal perspective. Cost year 1992/3. **Source of funding** Not reported		specific) estimates of unit costs • Alternative estimates of economic impact also were derived after adjustment for differences in practice patterns • To facilitate comparisons of findings across countries, we converted costs expressed in European currencies to US dollars using purchasing power parities • The components of costs included personnel, drugs other than antibiotics, diagnostic procedures, hotel (e.g. catering, cleaning), equipment and maintenance, and overheads • In the UK the median estimate from 3 CF centres (London, Northern Ireland and North-West England) were used to calculate daily costs (£200) • If an antibiotic that was prescribed in the US trial was unanavaliable locally, the lowest price of a commonly used alternative was used			used for cost build up • Uncertainty not sufficiently assessed, e.g. 95% CIs not reported **Other information** Practice-adjustment analyses were only undertaken for Italy and France in the likelihood of hospitalisation for a RTI as these patients were believed to be treated as outpatients rather than inpatients.

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
		instead, or excluded if one could not be identified • rhDNase was not a marketed product at the time these analyses were undertaken, the price is therefore unknown and not included in the analysis **Other data sources e.g. transition probabilities** NA			
Full citation Christopher, F., Chase, D., Stein, K., Milne, R., rhDNase therapy for the treatment of cystic fibrosis patients with mild to moderate lung disease, Journal of Clinical Pharmacy & Therapeutics, 24, 415-26, 1999 **Ref Id** 360606 **Economic study**	**Study dates** Not reported **Intervention** Daily 2.5mg rhDNase **Comparison(s)** Placebo	**Source of effectiveness data** Fuchs et al. 1992 was the only trial identified from their search that had a duration greater than 14 days. This was a large, multi-centre, randomised, double-blind, placebo controlled trial in the US over a 24-week period. **Source of cost data** • Treatment for one year of 2.5mg rhDNase daily £7,442 per patient based on the BNF 1998. • Saving from reduced antibiotic use not	**Time horizon and discount rate** • Time horizon: lifetime. • Discount rate: costs 6% and benefits 0%, but varied in sensitivity analysis. **Method of eliciting health valuations (if applicable)** NA	**Cost per patient per alternative** Average savings of £1,746 per patient from reduced hospitalisations over a 6-month period. **Effectiveness per patient per alternative** Continued use of rhDNase over the lifetime of a CF patient may increase their life expectancy by 2 years in all patients, or 7 in years in the subgroup. **Incremental cost-effectiveness** Not reported. **Other reporting of results** <u>1. All patients</u> Discounted costs per life year gained £52,550, assuming	**Limitations** • Assumed that once FEV dropped below 28% death would occur, whereas in clinical practice today these patients may undergo the cost of a lung-transplant which would increase their length and quality of life • Assumptions for disease progression and survival may reflect outdated practices and

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
type Cost-effectiveness analysis **Country(ies) where the study was done** Clinical effectiveness data taken from a US trial, but modelling undertaken from a UK perspective **Perspective & Cost Year** UK NHS non-societal perspective. Cost year unclear, cots taken from BNF 1998 and 1996/7 ERC costs for hospitalisations **Source of funding** Not reported		included as Fuchs et al. 1994 relates to the US and does not report the proportion given orally or intravenously, also note that practices may not be generalizable to the UK. • Fuchs et al. 1994 reported a mean saving of 1.3 hospital days over a 6-month period, this was translated into an average savings of £1,746 per patient responding to rhDNase based on 1996/7 ECR costs of average CF inpatient stays within the former South and West region. **Other data sources e.g. transition probabilities** NA	**Modelling approach** Two populations: 1. All patients • FEV declines at a rate of 4.2% per year from 100% of predicted value at birth to the of 13, then the rate of decline diminishes to 2.77% per year (Konstan et al. 1995) • Initial FEV of patients starting treatment is 61.1% of predicted (Fuchs et al. 1994) • Once FEV falls to this level all patients would be started on rhDNase (Fuch et al. 1994) • Patients reciving rhDNase would have an FEV 5.8% higher than they would have had otherwise throughout the course of	that patients were treated for 30 years, from the age of 11 until death at 41, with 2 life years gained from the continuous use of rhDNase, and allowing for savings over the first year of treatment. <u>2. Subgroup</u> Discounted costs per life year gained £16,110, assuming that patients were treated for 37 years, from the age of 8 until death at 45, with 7 life years gained from the continuous use of rhDNase, and allowing for savings over the first year of treatment. **Uncertainty** Explored changing the rate of decline in FEV, initial FEV, and the mean % improvement in FEV with rhDNase treatment. Varied the length of treatment and discount rate for costs and benefits.	underestimate their effects in clinical practice today • NICE reference case specifies a discount rate of 3.5% rather than 6% used in the model - a higher rate will underestimate the costs • Clinical outcomes based on a 24-week trial, there is no evidence to show these improvements can be sustained over a patients lifetime • Only rhDNase treatments costs and cost savings from hospitalisation were included (outpatients visits, HCP contacts, day case visits, antibiotic treatment were not included) **Other information** <u>1. All patients, sensitivity analysis</u>

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
			treatment (Fuchs et al. 1994) • Death would occur in the year FEV falls <28% of predicted (Konstan et al. 1995) • Given those assumptions the continued use of rhDNase over the lifetime of a CF patient may increase their life expectancy by 2 years 2. Subgroup of patients where initial FEV is ≤70% (and who demonstrate a sustained improvement in FEV of ≥10%) Same assumptions above plus: • Once FEV fell to 70% of predicted rhDNase would be introduced into the treatment regimen • Patients		• Although 2 life years are gained, the length of treatment varies from 9 to 39 years, ranging the cost per life year gained from £25,080 (9 years) to £57,220 (39 years) • If costs and benefits are discounted at 6%, the cost per life year gained ranges from £39,980 (9 years) to £523,780 (39 years) • If costs are discounted at 6% and benefits at 3%, the cost per life year gained ranges from £175,930 (9 years) to £175,930 (39 years) <u>2. Subgroup, sensitivity analysis</u> • Sensitivity analysis shows between 3

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
			receiving rhDNase would have an FEV 20% higher than they would have had otherwise • Given those assumptions the continued use of rhDNase over the lifetime of a CF patient may increase their life expectancy by 7 years		and 6 life years are gained with continuing use, ranging the cost per life year gained from £17,940 (6 life years gained with 32 years of treatment) to £36,620 (3 life years gained with 34 years of treatment) • If costs and benefits are discounted at 6%, the cost per life year gained ranges from £109,190 (6 life years gained with 32 years of treatment) to £250,480 (3 life years gained with 34 years of treatment) • If costs are discounted at 6% and benefits at 3%, the cost per life year gained ranges from £44,840 (6 life years gained with 32 years of treatment) to

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
					£97,120 (3 life years gained with 34 years of treatment)
Full citation Schechter, M. S., Trueman, D., Farquharson, R., Higuchi, K., Daines, C. L., Inhaled Aztreonam Lysine versus Inhaled Tobramycin in Cystic Fibrosis. An Economic Evaluation, Annals of the American Thoracic Society, 12, 1030-8, 2015 **Ref Id** 398897 **Economic study type** Cost-utility analysis **Country(ies) where the study**	**Study dates** Clinical taken from Asseal 2013 with a 12 month study duration **Intervention** Aztreonam **Comparison(s)** Inhaled tobramycin	**Source of effectiveness data** Asseal 2013 **Source of cost data** • drug costs from FirstDataBank • additional antibiotics inflated form OptimumInsight • hospitalisation costs inflated from Briesacher 2011 • lung transplant costs inflated from Amaoutakis 2011 • clinic visits inflated from O'Sullivan 2011 **Other data sources e.g. transition probabilities** • Kerem estimate a hazard ratio of 1.8 (95% confidence interval, 1.7–2.0) associated with	**Time horizon and discount rate** • Time horizon: 3 years • Discount rate: 3% • Cost year: 2013/14 **Method of eliciting health valuations (if applicable)** • Tappenden used data from Bradley to estimate EQ-5D based on FEV_1% predicted in patients with CF as follows: $FEV_1 > 70\%$ predicted, EQ-5D = 0.864; FEV_1 40–79% predicted, EQ-5D = 0.810; $FEV_1 < 40\%$ predicted, EQ-	**Cost per patient per alternative** Primary analysis, 3 year estimated costs Aztreonam; nebulised tobramycin; increment of aztreonam over tobramycin • Drug costs: $98,558; $107,581; −$9,023 • Hospitalisations: $47,762; $72,228; -$24,465 • Lung transplant: $55,130; $61,217; $6,087 • Routine resource use: $2,262; $2,247; $15 • Additional antibiotics: $22,639; $25,026; -$2,387 • Total costs: $226,352; $268,298; -$41,947 **Effectiveness per patient per alternative** Primary analysis, 3 year estimated costs Aztreonam; nebulised tobramycin; increment of aztreonam over tobramycin • QALYs: 1.916; 1.887; 0.0286 • Life-years: 2.513; 2.497; 0.0162 • Hospitalisations: 1.635; 2.473; -0.8377 **Incremental cost-effectiveness** • Aztreonam was associated with a total cost saving of $41,947 over 3 years compared with tobramycin solution for inhalation. • Aztreonam for inhalation solution was associated	**Limitations** • Cost sources not described and may be overestimated in a UK setting • It is unclear how hospitalisations rates were estimated from the data reported in Assael • TRAEs not considered **Other information** • The clinical trial had an open label extension during which all subjects received aztreonam for inhalation solution. Extrapolation of clinical data was required beyond 12 months in the aztreonam for inhalation solution

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was done US **Perspective & Cost Year** Perspective: third party payer in the US **Source of funding** Supported by Gilead Sciences		each reduction of FEV_1 by 10% predicted, so this was applied to the baseline risk to estimate 28-day probabilities of mortality for each health state • The probability of lung transplant for subjects in the severe health states was estimated from the 12-month cumulative incidence of lung transplant of 64.7% as reported by Thabut and converted to a 28-day probability assuming a constant risk, providing a probability of 7.7% in each cycle. For those patients who might receive a lung transplant, a 3-year risk of post-transplant survival of 67.8% was used. The 28-day probability of mortality was estimated from these data assuming a constant (exponential) risk of mortality, which yielded a per-cycle probability of mortality of 0.99% for patients in the post-transplant state. • Data from Assael were used to estimate the 28-day probabilities of	5D = 0.641. Linear interpolation from these estimates was used to predict EQ-5D scores in the FEV_1-defined health states that we used. • HRQOL measured with the CFQR by participants in the RCT by Assael, a scenario analysis that considered EQ-5D estimated using a mapping relationship between the CFQ-R and EQ-5D reported by Acaster and colleagues was also considered in scenario analysis • Exacerbation disutility (-0.174) taken from Tappenden and Bradley with a duration of 8 days • Lung transplant utility taken from	with a small increment in life-years (0.0162) and quality-adjusted life-years (0.0286) and fewer hospitalizations (−0.8377). • Overall, aztreonam for inhalation solution was associated with improved outcomes and reduced costs and is therefore dominant when compared with tobramycin solution for inhalation. <u>Incremental analysis of year 3 costs and outcomes, aztreonam vs. tobramycin</u> • Incremental cost; incremental benefit; ICER • QALYs: -$41,947; 0.0286; az dominant • LYs: -$41,947; 0.0162; az dominant • Hospitalisations: -$41,947; -0.8377; az dominant **Other reporting of results** • In all scenarios, the incremental cost per quality-adjusted life-year gained for aztreonam for inhalation solution was dominant compared with tobramycin solution for inhalation • The parameters to which the model was most sensitive were identified as the acquisition costs of aztreonam for inhalation solution and tobramycin solution for inhalation and the costs of exacerbation and lung transplant • The mean cost saving associated with aztreonam for inhalation solution was $41,856 (95% CrI, $10,491–$73,890), and the mean incremental utility gain was 0.0351 (95% CrI, −0.0246 to 0.0977). • The most commonly cited threshold used in the United States for cost-effectiveness analyses is $50,000per quality-adjusted life-year. For a cost-effectiveness threshold of $50,000 per quality-adjusted life-year, the probability that aztreonam for	arm and beyond 6 months in the tobramycin solution for inhalation arm of the model. • The probability of hospitalization was assumed to be independent of on–off treatment status and solely dependent on lung disease severity and treatment type (aztreonam for inhalation solution or tobramycin solution for inhalation). Hospitalization rates were estimated by pooling data over all assessments by lung disease severity for each treatment type. These risks were assumed to be constant by lung disease severity group for the duration of the model.

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		respiratory hospitalization	Busschbach for the procedure, then a utility of FEV 70-79 applied post transplant **Modelling approach** • Markov model with cycle lengths of 28 days, corresponding to the cyclical "on–off" regimen used in the prescription of both aztreonam and tobramycin • Patients can remain in the same FEV_1-defined health state, move to an adjacent health state, experience a lung transplant, or die • Patients were assumed to be exposed to a constant risk of a lung transplant if their FEV_1 fell below 30% , and	inhalation solution would be considered cost-effective versus tobramycin solution for inhalation is 99.5%. **Uncertainty** • Scenario analyses were conducted to assess the impact of varying key assumptions on the final model results • Probabilistic sensitivity analysis was conducted based on Monte Carlo simulation techniques using 5,000 simulations • Univariate sensitivity analysis was performed whereby parameters were systematically varied between plausible values and parameters subsequently ranked by the magnitude of change in the net monetary benefit associated with aztreonam for inhalation solution, calculated at a willingness-to-pay threshold of $50,000. The results for the 10 most influential parameters as identified by this analysis are plotted on a tornado diagram	

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			patients who reached FEV_1 less than 30% were not permitted to return to a healthier state • Patients undergoing transplant were assumed to have a risk of perioperative mortality for one model cycle, after which surviving patients were assumed to move to a post-transplant state for the remainder of the model, with survival rates based on published estimates • There is no exacerbation health state • FEV health states were split into severe (3: 20 to 39%), moderate (3: 40 to 69%), mild (2: 70 to 89%) and normal (1: >90%) • Each FEV health		

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			state within those categories was split into 10% so there were a total of 9 FEV health states		