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ORIGINAL RESEARCH ARTICLE

An Early Health Economic Analysis of the Potential Cost Effectiveness of an Adherence Intervention to Improve Outcomes for Patients with Cystic Fibrosis

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Abstract

Background Cystic fibrosis (CF) negatively impacts upon health-related quality of life and survival. Adherence to nebulised treatments is low; improving adherence is hypothesised to reduce rates of exacerbation requiring intravenous antibiotics and lung function decline.

Objective A state transition model was developed to assess the cost effectiveness of an intervention aimed at increasing patient adherence to nebulised and inhaled antibiotics compared with current CF care, in advance of the forthcoming CFHealthHub randomised controlled trial (RCT).

Methods The model estimated the costs and health outcomes for each option from the perspective of the UK National Health Service and Personal Social Services over a lifetime horizon. Health gains were valued in terms of quality-adjusted life-years (QALYs) gained. Forced expiratory volume in 1 second (FEV_1) trajectories were predicted over three lung function strata: (1) FEV_1 $\geq$70%, (2) FEV_1 40–69% and (3) FEV_1 <40%. Additional states were included to represent 'post-lung transplantation' and 'dead'. The model was populated using CF Registry data, literature and expert opinion. Costs were presented at 2016 values. Uncertainty was assessed using deterministic and probabilistic sensitivity analyses.

Results If effective, the adherence intervention is expected to produce an additional 0.19 QALYs and cost savings of £64,078 per patient. Across all analyses, the intervention dominated current care. Over a 5-year period, the intervention is expected to generate cost savings of £49.5 million for the estimated 2979 patients with CF with *Pseudomonas aeruginosa* currently aged $\geq$16 years in the UK. If applied to a broader population of adult patients with CF receiving any nebulised therapy, the expected savings could be considerably greater.

Conclusions If effective, the adherence intervention is expected to produce additional health gains at a lower cost than current CF care. However, the economic analysis should be revisited upon completion of the full RCT. More generally, the analysis suggests that considerable gains could be accrued through the implementation of adherence interventions that shift care from expensive hospital-based rescue to community-based prevention.

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Key Points for Decision Makers

Based on a pre-trial analysis of the CFHealthHub study, the use of an effective adherence intervention for cystic fibrosis (CF) is expected to produce an additional 0.19 quality-adjusted life-years (QALYs) and cost savings of £64,078 per patient compared with current CF care. Over a 5-year period, this corresponds to cost savings of approximately £49.5 million for the estimated 2979 patients with CF with *Pseudomonas aeruginosa* currently aged ≥16 years in the UK.

If the adherence intervention benefits a broader population of patients with CF who are receiving nebulised antibiotics and/or mucolytics and are aged ≥16 years (likely to represent approximately 5800 patients), the 5-year cost savings to the NHS are expected to be in excess of £96 million. Given existing uncertainty, it will be important to revisit this economic analysis upon completion of the full CFHealthHub randomised controlled trial.

1 Introduction

Cystic fibrosis (CF) is an inherited condition characterised by the abnormal transport of chloride ions (Cl^-) across transporting epithelia. This leads to the production of thick sticky mucus in the lungs, pancreas, liver, intestine and reproductive tract and increased salt content in sweat. More than 10,000 children and adults in the UK have CF [1]. Whilst CF limits life expectancy, survival is increasing, and approximately 6475 patients with CF in the UK were aged >16 years in 2015 [1]. Alongside other problems such as poor digestion, patients with CF are susceptible to lung infections, particularly with *Pseudomonas aeruginosa*. This is thought to be because the thick mucus makes it difficult for the body to clear inhaled bacteria and because people with CF have an increased airway inflammatory response to pathogens [2]. People with CF often develop intermittent infections during childhood that can be treated and even eradicated with nebulised or inhaled antibiotics. However, as infection develops, patients may reach a chronic stage whereby eradication is no longer possible because of the formation of biofilms [3]. In such cases, ongoing inhaled antibiotic treatment must be continued permanently. Patients commonly also require other treatments, including inhaled mucolytics, bronchodilators, steroids and physiotherapy [1]. Treatment is time consuming and burdensome [4], with administration of nebulised antibiotics taking up to 1 h per day whilst patients are well and longer during periods of ill health. In addition, patients also experience pulmonary exacerbations that require treatment with intravenous antibiotics administered either at home or in hospital. In either case, this treatment compromises the patient's ability to attend school or work and leads to increased healthcare costs.

Adherence to preventive nebulised CF treatments has been estimated at 48% on the basis of medication possession ratio (MPR) data in 3287 people with CF aged ≥6 years in the USA [5]. This is a measure of persistent adherence because these are chronic medications that are taken long term [6]. These data also showed that adherence was inversely related to age. Importantly, MPR measures only medication collected from the pharmacy and cannot measure whether that medication is ever taken. Objective UK data using chipped nebulisers in adults goes beyond the coarse MPR adherence metric to determine objectively how much treatment is actually taken. These data suggest a lower median adherence rate of 36% in nebulisers that are brought to clinic to be downloaded [7]. It is also important to ensure that estimated adherence rates take into account the patient's clinical status ('normative adherence') and includes both nebulisers brought to clinic and the more difficult-to-obtain nebulisers left at home; UK data reported by Hoo et al. [8] suggest that when all nebulised devices are included, normative adherence in adult clinics may be as low as 33%.

Treatments only work if they are taken, and estimates of drug effectiveness are usually derived from randomised controlled trials (RCTs) wherein strict inclusion criteria and trial procedures typically produce high adherence rates. Pugatsch et al. [9] recently reviewed adherence to CF treatments within clinical trials and reported an adherence rate of 80% as an aggregate estimate across the population over the entire duration of the studies (mean duration 7.3 months; range 2–24). The methodology for adherence measurement varied between trials but was typically undertaken at frequent intervals across the trials and can be considered a measure of persistent adherence [6]. Although there was a tendency for some reduction over time, adherence remained high across all phases of follow-up. Based on MPR data, it has been shown that patients with CF with poor adherence (MPR < 50%) have significantly higher healthcare costs than patients with good adherence (MPR > 80%); most of the excess costs in poor adherers are related to hospital admission for intravenous rescue therapy to treat pulmonary exacerbations [5]. Demonceau et al. [10] conducted a meta-analysis assessing feedback of objective adherence data in various conditions across 5237 patients; this study demonstrated that such feedback could increase adherence by around 20%, with a further 8% improvement if simple problem solving was added.

The ongoing CFHealthHub ACtiF (Adherence to treatment in adults with Cystic Fibrosis) trial is currently assessing an intervention to improve outcomes for patients with CF by empowering self-management and improving adherence to nebulised therapy via the use of chipped nebulisers with the capacity to directly monitor adherence levels, combined with an intervention to support problem solving, habit formation and self-efficacy undertaken by a member of the multidisciplinary team at regular appointments [11]. The hypothesis underpinning this RCT is that increasing adherence will reduce the number of exacerbations experienced by patients with CF. Reducing the number of exacerbations experienced by patients with CF may also impact on their rate of lung function deterioration.

This paper presents an early health economic evaluation of the expected cost effectiveness of the adherence intervention compared with current clinical care in advance of the completion of the full CFHealthHub ACtiF RCT (due to complete in September 2019). More generally, this analysis provides a formal quantification of the potential gains that could be accrued by improving disease control in CF through improved adherence.

2 Methods

2.1 Scope of the Analysis

A model-based cost-utility analysis was undertaken to assess the incremental cost effectiveness of the adherence intervention versus standard care in adult patients with CF receiving traditional nebulised or dry powder inhaled (DPI) antibiotics from the perspective of the UK National Health Service (NHS) and Personal Social Services (PSS) over a lifetime horizon. The intervention relates to a newly developed nebuliser with the capacity to monitor and report adherence levels (developed as part of the CFHealthHub ACtiF programme [11]) combined with a behavioural intervention undertaken by a physiotherapist at regular appointments. Health benefits are assessed in terms of quality-adjusted life-years (QALYs) gained. All costs and health outcomes were discounted at a rate of 3.5% per annum [12]. Costs were valued at 2016 values.

2.2 Model Structure

The analysis used a state transition approach based on the structure of a previously published health economic model developed to assess the cost effectiveness of DPIs for patients with CF with chronic *P. aeruginosa* [13, 14]. The model was populated using analyses of individual patient data (IPD) from the UK CF Registry [15], literature and expert opinion. The model estimates forced expiratory volume in 1 s (FEV_1) percent predicted trajectories over three strata of lung function: (1) $FEV_1 \geq 70\%$, (2) FEV_1 40–69% and (3) $FEV_1 < 40\%$ (Fig. 1). Additional health states are included to represent 'post-lung transplantation' and 'dead'. During each annual cycle, patients may remain in their current FEV_1 state, transit to an improved or worsened FEV_1 state or die. A small proportion of patients with $FEV_1 < 40\%$ may undergo lung transplantation and do not subsequently receive further nebulised/DPI treatment. Health-related quality of life (HRQoL) is modelled according to FEV_1 stratum and transplant history, with disutilities applied according to the proportion of time spent receiving intravenous antibiotics to manage CF exacerbations. A half-cycle correction was applied to account for the timing of events. Total QALYs are calculated as the total sojourn time in each health state weighted by state-specific utility scores, less any QALY losses resulting from exacerbations. The model conservatively assumes there is no survival difference between the intervention and comparator groups. Costs include UK CF tariff treatment costs, high-cost drug acquisition, costs of days spent in hospital receiving intravenous antibiotics and associated intravenous antibiotic acquisition, transplantation costs and those associated with the adherence

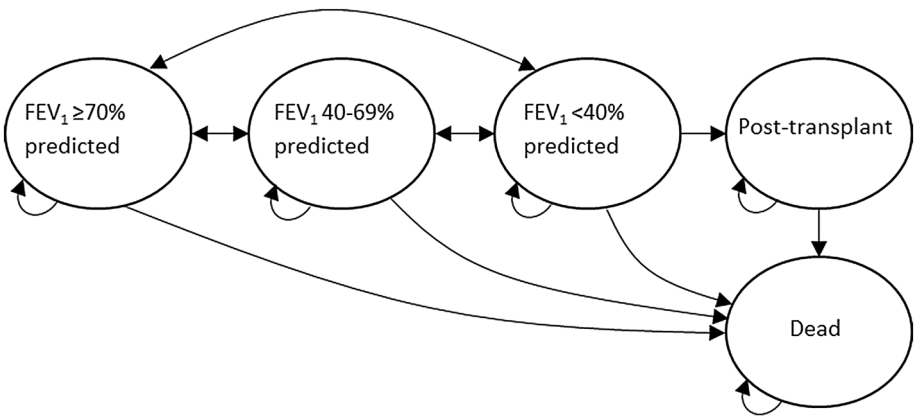

Fig. 1 Model structure. *FEV_1* forced expiratory volume in 1 second

intervention. All other costs were assumed to be captured in the CF banding tariff [16].

The model employs the following assumptions:

- Patients in any FEV_1 stratum can progress/regress to any other FEV_1 stratum.
- Reductions in exacerbations impact upon progression rates between FEV_1 strata.
- The probability of experiencing exacerbations differs by FEV_1 stratum.
- A small proportion of patients with $FEV_1 < 40\%$ undergo lung transplant, whereas those ineligible for transplant continue to receive nebulised/DPI therapy.
- Reductions in lung function and the incidence of exacerbations impact upon HRQoL.
- The adherence intervention will impact upon the incidence of exacerbations and FEV_1 transitions.
- Exacerbation rates and transition rates between FEV_1 strata are time invariant.
- The costs of 'high-cost therapies' are independent of adherence to those therapies.

2.3 Evidence Used to Inform the Model Parameters

Model parameters and their associated distributional properties are summarised in Table 1.

2.3.1 Patient Characteristics

The population is assumed to be aged 16 years at model entry. The initial distribution of patients across the health states was based on recorded FEV_1 in 2013 from the CF Registry (the most recent year available for the analysis).

2.3.2 Transition Probabilities

Transition probabilities were derived from IPD from the CF Registry for a total of 10,344 patients between 2007 and 2013 [15]. The overall dataset was restricted to patients who had been recorded (at least once) as having 'intermittent' or 'chronic' *P. aeruginosa* status ($n = 7518$). Of these patients, 53% were male, and their average age on first appearing in the 2007–2013 dataset was 19 years (range 0–82). At baseline, the proportion of patients in each FEV_1 stratum was as follows: $FEV_1 < 40\% = 0.13$, FEV_1 40–69% = 0.32, $FEV_1 \geq 70\% = 0.55$. Of these, 6788 had at least one recorded FEV_1 assessment and 1700 had measures for all 7 years. Longitudinal regression was undertaken using the methods described by Jung [23]. This involved the estimation of a series of ordered logit models, which give the log odds of being in a given FEV_1 group post-transition, given the time (in days) between observations, the annual rate of days in hospital receiving intravenous antibiotics and the patient's age. One model was estimated for each of three possible FEV_1 starting states, and the model outputs were converted into annual probabilities. This approach allowed for the inclusion of patients who had between two and seven entries in the registry, even if there were gaps before, between or after review entries. Patients who left the registry were excluded from the analysis. The time variable (days since last visit) allowed for the calculation of annual transitions despite the fact that sample intervals varied in the raw registry data. The lagged rate of intravenous days variable allowed for the investigation of the effect of exacerbations on FEV_1 progression. A number of models were tested with both age and sex as covariates. Age was statistically significant in most models, but sex was not significant, therefore age was retained in the final model.

2.3.3 Mean Days Receiving Intravenous Antibiotics per Year

Mean days in hospital or at home receiving intravenous antibiotics for each FEV_1 group were estimated from the same group of patients with *P. aeruginosa* in the CF Registry used to derive transition probabilities [15].

2.3.4 Effectiveness of the Adherence Intervention

The intervention was assumed to reduce the number of days receiving intravenous antibiotics, leading to changes in the transition rates between the FEV_1 strata. The CFHealthHub ACtiF trial is powered to detect a reduction of one exacerbation per annum, based on a previous trial of long-term inhaled hypertonic saline for CF [17]. This treatment effect is assumed to reflect the minimum clinically important difference. Assuming one exacerbation is equivalent to 14 days receiving intravenous antibiotics at home or in the hospital [24, 25], when applied to the whole CF Registry cohort with *P. aeruginosa*, this equates to a 55% reduction in days spent receiving intravenous antibiotics. Uncertainty surrounding the relative risk reduction in days receiving intravenous antibiotics was assumed to broadly reflect that observed in the trial by Elkins et al. [17], but the 95% confidence interval (CI) was widened to account for additional uncertainty surrounding the effectiveness of the adherence intervention (mean relative risk 0.45, standard error 0.09). Post-intervention exacerbation rates were also applied to the logit models to derive FEV_1 transition probabilities for the adherence intervention.

2.3.5 Cystic Fibrosis Mortality

The CF Registry does not include sufficient data to allow for the robust derivation of estimates of long-term survival

Table 1 Model parameters

Parameter	Distribution	Parameter 1	Parameter 2	Mean	Source
General parameters					
Time horizon (years)	NA	–	–	84	NA
Cycle length (years)	NA	–	–	1	NA
Start age (years)	NA	–	–	16	Assumption
Discount rate QALYs	NA	–	–	3.50%	NICE methods guide [12]
Discount rate costs	NA	–	–	3.50%	
Initial distribution					
$FEV_1 \geq 70\%$	Dirichlet	2891.00	5715.00	0.51	CF Registry dataset [15]
FEV_1 40–60%	Dirichlet	1965.00	5715.00	0.34	
$FEV_1 < 40\%$	Dirichlet	859.00	5715.00	0.15	
Post-transplant	–	–	–	0	Assumption
Dead	–	–	–	0	
Transition probabilities: current clinical care					
$FEV_1 \geq 70$ to $\geq 70\%$	Dirichlet	6056.33	6999.00	0.87	Logit model fitted to CF Registry dataset [15]
$FEV_1 \geq 70$ to 40–60%	Dirichlet	920.69	6999.00	0.13	
$FEV_1 \geq 70$ to <40%	Dirichlet	21.98	6999.00	0.00	
FEV_1 40–60 to $\geq 70\%$	Dirichlet	502.08	3743.00	0.13	
FEV_1 40–60 to 40–60%	Dirichlet	2860.77	3743.00	0.76	
FEV_1 40–60 to <40%	Dirichlet	380.15	3743.00	0.10	
$FEV_1 < 40$ to $\geq 70\%$	Dirichlet	35.37	1350.00	0.03	
$FEV_1 < 40$ to 40–60%	Dirichlet	185.16	1350.00	0.14	
$FEV_1 < 40$ to <40%	Dirichlet	1129.47	1350.00	0.84	
Transition probabilities: post-intervention					
$FEV_1 \geq 70$ to $\geq 70\%$	Dirichlet	6100.83	6999.00	0.87	Logit model fitted to CF Registry data [15] including ACtiF trial power calculation [11]
$FEV_1 \geq 70$ to 40–60%	Dirichlet	877.38	6999.00	0.13	
$FEV_1 \geq 70$ to <40%	Dirichlet	20.79	6999.00	0.00	
FEV_1 40–60 to $\geq 70\%$	Dirichlet	545.51	3743.00	0.15	
FEV_1 40–60 to 40–60%	Dirichlet	2849.04	3743.00	0.76	
FEV_1 40–60 to <40%	Dirichlet	348.45	3743.00	0.09	
$FEV_1 < 40$ to $\geq 70\%$	Dirichlet	34.65	1350.00	0.03	
$FEV_1 < 40$ to 40–60%	Dirichlet	182.04	1350.00	0.13	
$FEV_1 < 40$ to <40%	Dirichlet	1133.30	1350.00	0.84	
Transplant rate					
Probability transplant/year ($FEV_1 < 40\%$)	Normal	0.004	0.000	0.004	Based on CF Registry [1] and US CF Foundation
IV days (exacerbations): baseline					
$FEV_1 \geq 70\%$	Beta	1802.23	42,817.94	0.04	Observed data from CF registry dataset [15]
FEV_1 40–60%	Beta	3134.66	32,608.88	0.09	
$FEV_1 < 40\%$	Beta	1184.13	6181.86	0.16	
IV days (exacerbations): post-intervention					
Relative risk of exacerbation requiring IV treatment	Log normal	0.45	0.09	0.45	Power calculation based on Elkins et al. [17]. Additional uncertainty included in 95% CI
IV days: $FEV_1 \geq 70\%$	NA	–	0.02	–	Calculated using baseline IV days and relative risk of exacerbation requiring IV treatment

Table 1 continued

Parameter	Distribution	Parameter 1	Parameter 2	Mean	Source
IV days: FEV_1 40–60%	NA	–	0.04	–	
IV days: $FEV_1 < 40\%$	NA	–	0.07	–	
Health-related quality of life					
Utility $FEV_1 \geq 70\%$	Beta	108.52	17.08	0.86	Bradley et al. [18]
Disutility $FEV_1 \geq 70$ to 40–69%	Beta	4.11	72.01	0.05	
Disutility FEV_1 40–69 to <40%	Beta	12.60	61.51	0.17	
Disutility IV exacerbation	Beta	3.48	16.53	0.17	
Utility: post-transplant	Beta	319.31	65.40	0.83	Anyanwu et al. [19]
Survival					
Gompertz: constant	Normal	0.004	0.00	0.00	Parametric survivor function fitted to data reported by Dodge et al. [20]
Gompertz: Gamma	Normal	0.06	0.01	0.06	
CF banding by FEV_1 %					
$FEV_1 \geq 70\%$—Proportion band 1	Dirichlet	886	4418.00	0.20	CF Registry dataset [15]
$FEV_1 \geq 70\%$—Proportion band 1a	Dirichlet	83.00	4418.00	0.02	
$FEV_1 \geq 70\%$—Proportion band 2	Dirichlet	1063.00	4418.00	0.24	
$FEV_1 \geq 70\%$—Proportion band 2a	Dirichlet	1497.00	4418.00	0.34	
$FEV_1 \geq 70\%$—Proportion band 3	Dirichlet	799.00	4418.00	0.18	
$FEV_1 \geq 70\%$—Proportion band 4	Dirichlet	75.00	4418.00	0.02	
$FEV_1 \geq 70\%$—Proportion band 5	Dirichlet	15.00	4418.00	0.00	
FEV_1 40–60%—Proportion band 1	Dirichlet	115.00	2290.00	0.05	
FEV_1 40–60%—Proportion band 1a	Dirichlet	28.00	2290.00	0.01	
FEV_1 40–60%—Proportion band 2	Dirichlet	250.00	2290.00	0.11	
FEV_1 40–60%—Proportion band 2a	Dirichlet	807.00	2290.00	0.35	
FEV_1 40–60%—Proportion band 3	Dirichlet	787.00	2290.00	0.34	
FEV_1 40–60%—Proportion band 4	Dirichlet	247.00	2290.00	0.11	
FEV_1 40–60%—Proportion band 5	Dirichlet	56.00	2290.00	0.02	
$FEV_1 < 40\%$—Proportion band 1	Dirichlet	20.00	947.00	0.02	
$FEV_1 < 40\%$—Proportion band 1a	Dirichlet	6.00	947.00	0.01	
$FEV_1 < 40\%$—Proportion band 2	Dirichlet	60.00	947.00	0.06	
$FEV_1 < 40\%$—Proportion band 2a	Dirichlet	234.00	947.00	0.25	

Table 1 continued

Parameter	Distribution	Parameter 1	Parameter 2	Mean	Source
$FEV_1 < 40\%$—Proportion band 3	Dirichlet	310.00	947.00	0.33	
$FEV_1 < 40\%$—Proportion band 4	Dirichlet	225.00	947.00	0.24	
$FEV_1 < 40\%$—Proportion band 5	Dirichlet	92.00	947.00	0.10	
High-cost drug use					
Dornase alpha	Beta	3949.00	2660.00	0.60	CF Registry dataset [15]
Tobramycin	Beta	779.00	5830.00	0.12	
Aztreonam	Beta	235.00	6374.00	0.04	
Colistimethate sodium (Colomycin)	Beta	2555.00	4054.00	0.39	
Colistimethate sodium (Promixin)	Beta	1602.00	5007.00	0.24	
Tobi + Podhaler	Beta	779.00	5830.00	0.12	
CF banding costs					
Cost band 1	Fixed	£5033	–	£5033	NHS England Monitor report 2016 Annex A [16]
Cost band 1a	Fixed	£7447	–	£7447	
Cost band 2	Fixed	£7447	–	£7447	
Cost band 2a	Fixed	£12,036	–	£12,036	
Cost band 3	Fixed	£18,422	–	£18,422	
Cost band 4	Fixed	£33,224	–	£33,224	
Cost band 5	Fixed	£40,054	–	£40,054	
Drug costs					
Dornase alpha	Fixed	£6044.04	–	£6044.04	British National Formulary 2016 [21]
Tobramycin	Fixed	£6016.25	–	£6016.25	
Aztreonam	Fixed	£14,228.64	–	£14,228.64	
Colistimethate sodium (Colomycin)	Fixed	£2366.82	–	£2366.82	
Colistimethate sodium (Promixin)	Fixed	£8181.60	–	£8181.60	
Tobi + Podhaler	Fixed	£11,674.96	–	£11,674.96	
Adherence intervention: marginal costs					
Once-only data transfer hardware	Fixed	£121.20	–	£121.20	Personal communication—Martin Wildman, Sheffield Teaching Hospitals, England, 2016
Annual data transfer	Fixed	£158.40	–	£583.44	
Other costs					
Cost IV day	Normal	£361.68	£77.48	£361.68	NHS reference costs 2014/15—Long-stay bronchiectasis, CC score 0 [22]
Proportion of IV days in hospital	Beta	93,455.00	78,452.00	0.54	Personal communication—Tim Gleeson, Sheffield Teaching Hospitals, England, 2016
Cost of IV ceftazidime and tobramycin per day	Fixed	£71.99	–	£71.99	Personal communication—Martin Wildman, Sheffield Teaching Hospitals, England, 2015
Cost transplant	Normal	£40,000.00	£4000.00	£40,000.00	Personal communication—Kim Cox, NHS England, 2015

CC comorbidities and complications, *CF* cystic fibrosis, *CI* confidence interval, *FEV_1* forced expiratory volume in 1 s, *IV* intravenous, *NA* not applicable, *NHS* UK National Health Service, *NICE* National Institute for Health and Care Excellence, *QALY* quality-adjusted life year

for patients with CF [15]. Instead, survival estimates were based on an analysis reported by Dodge et al. [20]. This study reported survival data up to the end of 2003 for all subjects with CF born in the UK in the period 1968–1992 collated via active enquiry of CF clinics and other hospital consultants. The published survival curves for males and females were digitised, and patient-level time-to-event data were reconstructed using methods reported by Guyot et al. [26]. Parametric survivor functions (exponential, log normal, log logistic, Weibull, Gompertz and generalised Gamma) were fitted to the replicated data to extrapolate beyond the observed follow-up period. Model discrimination was undertaken using visual inspection, an examination of the goodness-of-fit statistics for each survivor function [the Akaike Information criterion (AIC) and the Bayesian Information Criterion (BIC)] and subjective clinical judgement regarding the plausibility of the extrapolated portion of each parametric curve. On the basis of clinical plausibility, the Gompertz survivor function was selected for use in the model. Uncertainty surrounding the parameters of the survivor function was modelled using independent normal distributions with the 95% CI width calibrated such that it was similar to that observed for patients in the current CF Registry population. The same function was applied to the intervention and comparator groups, hence the adherence intervention is not assumed to impact on patient survival.

2.3.6 Probability of Transplantation

The probability that a patient with FEV_1 <40% will undergo a lung transplant during each cycle was estimated based on data from the UK CF Registry [1] and the US Cystic Fibrosis Foundation, assuming a 2–3% lifetime probability of undergoing lung transplantation [13, 14].

2.3.7 Health-Related Quality of Life

The selection of studies used to inform HRQoL parameters within the model was based on a previous systematic review [13]. Health state utilities associated with each FEV_1 stratum and the disutility associated with exacerbations were based on a UK utility valuation study reported by Bradley et al. [18]. Within this study, the three-level EuroQol-5 Dimensions (EQ-5D) and the Cystic Fibrosis Questionnaire-Revised (CFQ-R) were administered to patients aged ≥16 years with CF and chronic *P. aeruginosa* who were receiving nebulised or oral antibiotics. The utility score for patients who have undergone lung transplantation was taken from a cross-sectional utility valuation study involving three-level EQ-5D assessments in patients awaiting lung transplantation and transplant recipients attending follow-up clinics in the UK [19].

2.3.8 Resource Costs

The model included costs associated with CF tariff banding, high-cost antibiotic therapies, days in hospital receiving intravenous antibiotics, intravenous antibiotics, transplantation and the adherence intervention. The proportion of patients in each band of the CF tariff according to FEV_1 stratum were derived from the CF Registry [15]; banding tariff costs were taken from the latest NHS National Tariff [16]. Usage of specific antibiotic products was estimated from the CF Registry dataset [15]. The analysis assumed that patients were prescribed these treatments according to their licensed dosing schedules rather than according to patient adherence levels. Unit costs for nebulised and DPI antibiotics were derived from British National Formulary (BNF) 2016 [21]. Transplantation costs were based on personal communication (Kim Cox, NHS England; 2015). The costs of intravenous antibiotics (tobramycin and ceftazidime) were sourced from Sheffield Teaching Hospitals (Tim Gleeson; 2016; personal communication). The cost of a day in hospital receiving intravenous antibiotics was based on NHS Reference Costs 2014–2015; as no inpatient costs relating to CF exacerbations were available, we assumed a daily cost associated with a long-stay inpatient admission for bronchiectasis with complications and comorbidity score of 0 (daily cost £361.68) [22]. The model assumes that 54% of days receiving intravenous antibiotics take place in hospital and the remaining 46% take place at the patient's home and do not lead to additional costs for the NHS (Tim Gleeson, Sheffield Teaching Hospitals, England; 2016; personal communication). The costs of the adherence intervention were assumed to include a once-only cost for data transfer hardware of £121.20 plus an ongoing annual data transfer cost of £583.44 per patient (Martin Wildman, Sheffield Teaching Hospitals, England; 2016; personal communication). The analysis assumed the training and implementation costs associated with the behavioural impact component of the adherence intervention would be absorbed into routine clinic appointments undertaken by CF healthcare practitioners. These costs have therefore been excluded.

2.3.9 Model Evaluation Methods

Cost effectiveness was expressed in terms of the incremental cost per QALY gained. Uncertainty surrounding the cost effectiveness of the adherence intervention was explored using deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). The PSA included all uncertain model parameters and was implemented using simple Monte Carlo sampling methods (2000 random iterations). DSAs were conducted to explore the impact of

alternative time horizons, assumptions of a less durable treatment effect, an assumption that the intervention impacted on exacerbation rates only, reduced impacts on exacerbation rates, and alternative assumptions regarding cost and utility parameters. In addition, a further scenario was conducted whereby treatment costs were calculated according to expected adherence levels in each group, based on Daniels et al. [7] (36% drug consumption in current CF care group) and Demonceau et al. [10] (63.7% drug consumption for the adherence intervention group).

2.3.10 Model Validation Methods

Several measures were taken to verify the implemented model and to the ensure the credibility of its underlying conceptual basis. These included internal peer review by clinical experts, scrutiny of the implemented model coding and formulae, checking the accuracy of all model inputs against sources, investigating potentially discrepant or unexpected results identified through black box testing and double programming of the deterministic model. Whilst the results of the CFHealthHub ACtiF trial will not be available until at least September 2019, this evidence, once available, will allow the economic analysis to be updated using prospectively collected randomised data; this will also enable the comparison of the predictions of the pre-trial and post-trial analyses.

3 Results

3.1 Central Estimates of Cost Effectiveness

Table 2 presents the central estimates of cost effectiveness for the adherence intervention versus current CF care based on the probabilistic version of the model.

The probabilistic version of the model suggests that, if effective, the adherence intervention is expected to produce an additional 0.19 discounted QALYs per patient and cost savings of approximately £64,078 per patient over their remaining lifetime; hence, the adherence intervention is expected to dominate current care. The cost savings predicted by the model are driven by a small shift in CF banding resulting from improvements in predicted FEV_1 trajectory, together with a significant reduction in the expected number of days spent in hospital receiving intravenous antibiotics (accounting for savings of approximately £70,000 per patient). As shown in the cost-effectiveness plane (Fig. 2), whilst there is considerable uncertainty surrounding the health gains associated with the intervention, the probabilistic analysis consistently indicates that the adherence intervention is expected to produce substantial cost savings. Across willingness-to-pay thresholds of between £0 and £100,000 per QALY gained, the probability that the adherence intervention produces more net benefit than current care is expected to be 1.0.

3.2 Sensitivity Analysis Results

Across all of the DSAs, the adherence intervention is expected to dominate current care (Table 3). This includes the highly pessimistic situation whereby the costs of high-cost drugs were calculated exactly according to the level of patient adherence, based on the work of Daniels et al. [7] and Demonceau et al. [10]. Even in this unlikely scenario, the savings associated with avoided costs of days in hospital receiving intravenous antibiotics outweigh the additional costs of drug therapy due to increased patient adherence to nebulised and inhaled therapy. Assuming treatment costs are independent of adherence levels, the sensitivity analysis suggests that, over the course of 5 years, the model estimates discounted cost savings of £16,623 per patient; this is equivalent to approximately £49.5 million for the estimated 2979 patients with CF with *P. aeruginosa* currently aged ≥16 years in the UK. Should the intervention benefit a broader population of patients with CF receiving nebulised antibiotics and/or mucolytics and aged ≥16 years (likely to represent approximately 5800 patients), the 5-year cost savings to the NHS are expected to be in excess of £96 million.

4 Discussion

This study represents the first health economic analysis of an intervention targeted at increasing patient adherence to nebulised/DPI treatments in CF. The results of the analysis suggest the adherence intervention has the potential to

Table 2 Central estimates of cost-effectiveness (probabilistic)

Option	QALYs	Costs (£)	Incremental QALYs	Incremental costs (£)	Incremental cost per QALY gained
Adherence intervention	12.24	431,261	0.19	−64,078	Dominating
Current care	12.05	495,338	–	–	–

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

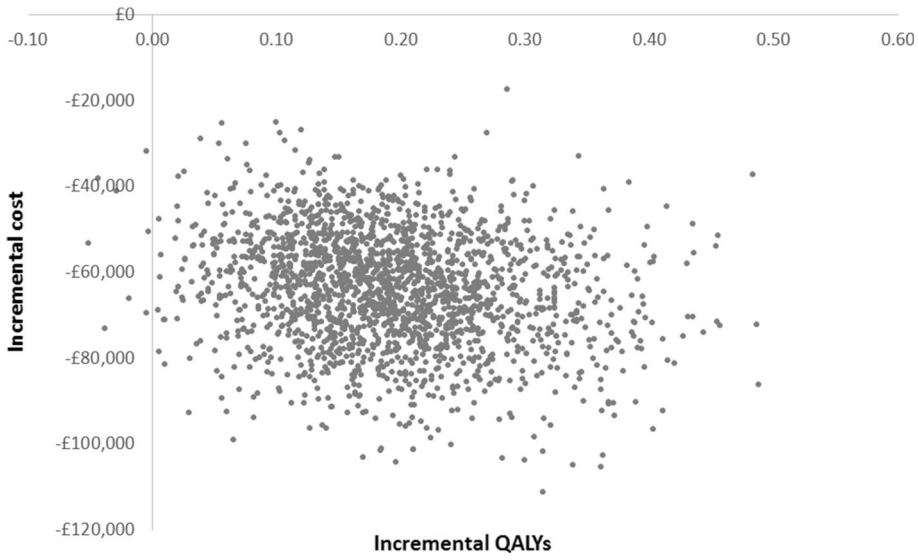

Fig. 2 Cost-effectiveness plane. *QALY* quality-adjusted life-year

Table 3 Deterministic sensitivity analysis results

Scenario	Adherence intervention versus current care		ICER
	Incremental QALYs	Incremental costs (£)	
Base case	0.19	−63,832	Dominating
Undiscounted results	0.34	−106,715	Dominating
Time horizon (years)			
5	0.04	−16,623	Dominating
10	0.08	−30,871	Dominating
20	0.15	−50,257	Dominating
Intervention impacts on intravenous days only	0.12	−59,314	Dominating
Treatment effect duration (years)			
5	0.06	−11,566.59	Dominating
10	0.10	−27,707.06	Dominating
10	0.16	−49,064.01	Dominating
25% reduction in exacerbation rate RR (RR reduction 0.58)	0.16	−47,213	Dominating
50% reduction in exacerbation rate RR (RR reduction 0.72)	0.13	−30,594	Dominating
Cost intravenous days halved	0.19	−38,263	Dominating
Cost of adherence intervention doubled	0.19	−54,796	Dominating
Intravenous disutility doubled	0.32	−63,832	Dominating
Intravenous disutility halved	0.13	−63,832	Dominating
Treatment costs assumed to exactly reflect patient consumption based on Daniels et al. [7] and Demonceau et al. [10]	0.19	−25,247	Dominating

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *RR* relative risk

produce considerable health gains and cost savings for the NHS, thereby dominating current CF care. The principal driver of the anticipated cost savings is the expected reduction in days in hospital receiving intravenous antibiotics. The sensitivity analysis suggests that, even under pessimistic assumptions regarding lower levels of effectiveness of the intervention and lower unit costs per day in hospital for intravenous antibiotics, the adherence intervention is expected to remain dominant. This suggests that, even if the CFHealthHub ACtiF trial does not meet its primary endpoint, the intervention may still produce cost savings for the health service.

Since this health economic analysis precedes the CFHealthHub ACtiF trial, there is considerable uncertainty

regarding whether the findings of the analysis will concord with the data that will be collected within the trial itself. Invariably, such early modelling analyses are subject to the risk of reaching erroneous conclusions and rely on a weaker evidence base than would be available had the full trial been completed. It is therefore important to consider these issues in the interpretation of the results of this analysis; these limitations are discussed briefly in the following sections.

4.1 Clinical Evidence to Support the Effectiveness of the Adherence Intervention

The most pertinent limitation of the evidence base is that the CFHealthHub ACtiF trial, which aims to assess the clinical benefit of the adherence intervention, has not yet completed. As such, there is currently no direct empirical evidence through which to quantify the benefits of the adherence intervention. Given this lack of evidence, the model uses the expected reduction in exacerbations used to inform the power calculations for the CFHealthHub ACtiF trial [11, 17] as the basis for modelling expected treatment effects. Whilst this estimate reflects a legitimate prior belief, and forms the basis of the hypothesis that will be tested within the trial, there is a possibility that the anticipated reduction in exacerbations could be higher or lower than predicted. Nonetheless, the economic analysis presented here has a wider relevance in quantifying the potential gains that could be accrued through the implementation of adherence interventions that shift care from expensive hospital-based rescue to more economical community-based prevention. This analysis may therefore be useful in supporting the development and evaluation of other adherence interventions within the NHS or across other healthcare systems.

4.2 Transition Probabilities and Exacerbation Rates are Assumed to Apply Indefinitely

The model uses a single matrix of probabilities describing the trajectories of lung function across three FEV_1 strata in each treatment group. Whilst age is included as a covariate in the logit regression analyses, these are treated as time-independent parameters within the health economic model. In reality, FEV_1 transitions may be time variant. Because long-term data on FEV_1 trajectories with and without the intervention are absent, the model assumes these trajectories remain constant with respect to time. However, it should be noted that the economic conclusions drawn from the analysis remain unchanged even if the intervention has no impact upon lung function decline (Table 3).

4.3 Treatment Effect Assumed to Apply Indefinitely

Given the preliminary nature of the health economic analysis and the current lack of evidence regarding the effectiveness of the adherence intervention, the model assumes that the treatment effect applies indefinitely over the patient's remaining lifetime. It may be the case that levels of adherence to antibiotic therapies may increase or wane over time following the introduction of the intervention. The sensitivity analysis suggests that both health gains and cost savings are expected to be reduced over shorter intervals, although the intervention is expected to remain dominant irrespective of the time horizon and assumptions regarding the durability of the treatment effect.

4.4 Limitations in Handling Cost Savings due to the Cystic Fibrosis Banding Tariff

Within the model, benefits and costs are captured through two different processes: (1) a direct reduction in the number of days spent receiving intravenous antibiotics and (2) the impact of reduced exacerbations on subsequent FEV_1 trajectory. In England, CF care is currently funded via a mandatory tariff for specialist commissioning, which is intended to reflect the severity of disease in individual patients; the UK CF banding tariff is intended to encapsulate both lung function and days receiving intravenous antibiotics. Consequently, an analysis that accounts only for changes in the CF tariff band would fail to fully reflect cost savings realised by the NHS due to fewer days spent in hospital receiving intravenous antibiotics; this would lead to an underestimate of the true cost effectiveness of the adherence intervention. Alternatively, an analysis that includes CF banding costs as well as costs of days in hospital receiving intravenous antibiotics, as has been assumed here, may overestimate the cost savings associated with reducing exacerbations. It is anticipated that the data collection mechanisms within the CFHealthHub ACtiF trial will allow for a more sensitive and accurate analysis of the true costs associated with the adherence intervention based on the direct modelling of FEV_1 status and CF banding categories.

4.5 Relationship between Treatment Costs and Patient Adherence

There is uncertainty regarding the relationship between the costs of treatment and patient adherence to those treatments. The base-case analysis assumes that antibiotic treatment costs borne by the NHS are independent of patient adherence levels. It is possible that increasing adherence levels will also lead to increases in total NHS

expenditure on antibiotic treatments: as patients become more adherent to therapy, they may require more frequent prescriptions. The consequence of this situation would be an increase in the total CF drugs bill, and the expected cost savings of increased adherence would be somewhat diminished. However, the sensitivity analyses indicate that, even in the presence of very pessimistic assumptions regarding the relationship between treatment adherence and treatment costs, specifically a scenario whereby treatment costs borne by the NHS exactly reflect patient consumption of those treatments, the adherence intervention is expected to remain cost saving (Table 3).

5 Conclusions

Based on an early health economic analysis using high-quality registry data [1, 15] and the estimated reduction in exacerbations used to inform the design of the CFHealthHub ACtiF trial [11], the adherence intervention is expected to produce additional health gains at a substantially lower cost than current CF care. The findings of the analysis should be revisited upon the completion of the full RCT. More broadly, the analysis suggests that considerable gains could be accrued through the implementation of adherence interventions that shift care from hospital-based rescue to community-based prevention.

Data Availability The model developed within this study is available from the corresponding author upon reasonable request. The authors confirm that all model inputs are presented in the paper.

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Author Contributions Paul Tappenden developed the health economic model. Susannah Sadler undertook the analyses of the CF Registry dataset. Martin Wildman advised on the design of the study and the evidence used to inform the model. All authors contributed to the preparation of this manuscript. Paul Tappenden will act as the overall guarantor for this work.

Compliance with Ethical Standards

Funding Dr Wildman has received support from Pari to speak at conferences about the importance of adherence and to travel to meetings with Pari about setting up a trial to understand whether increasing adherence improves outcomes in CF. He has also received funding from Philips to support research using the Ineb nebuliser to understand how the device can be used to measure adherence and received speaker fees from Forest to give independent talks at CF meetings around the UK about the importance of adherence. Paul Tappenden and Susannah Sadler have no conflicts of interest.

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