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Treatment preference amongst people with cystic fibrosis: the importance of reducing treatment burden

Rory A. Cameron, PhD, MScPH, Daniel Office, BSc, Jessie Matthews, MSc, Mark Rowley, Janice Abbott, PhD, Nicholas J. Simmonds, MD, Jennifer A. Whitty, PhD, Siobhán B. Carr, MBBS

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Short title: Treatment preference amongst people with cystic fibrosis

Rory A. Cameron, PhD, MScPH; Daniel Office, BSc; Jessie Matthews, MSc; Mark Rowley, Janice Abbott, PhD; Nicholas J. Simmonds, MD; Jennifer A. Whitty, PhD; and Siobhán B. Carr, MBBS

AFFILIATIONS

From the Norwich Medical School (R. Cameron and J. Whitty), University of East Anglia, Norwich, UK; the National Institute for Health Research, Applied Research Collaboration, East of England (R. Cameron and J. Whitty); the Adult Cystic Fibrosis Centre (D. Office, J. Matthews and N. Simmonds), Royal Brompton Hospital, London, UK; patient representative (M. Rowley); School of Psychology (J. Abbott), University of Central Lancashire, UK; the National Heart and Lung Institute (N. Simmonds and S. Carr), Imperial College, London, UK; Department of Paediatric Respiratory Medicine (S. Carr), Royal Brompton Hospital, London, UK; and Evidera Inc, London, UK (J. Whitty)

CORRESPONDENCE TO:

Rory A. Cameron, PhD, MScPH, Health Economics Group, Norwich Medical School, University of East Anglia, Norwich, Norfolk, NR4 7TJ, UK; rory.cameron@uea.ac.uk

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COMPETING INTERESTS

RC, DO, JM, JA, and JW report no competing interests. NS has received honoraria for lectures from Vertex, Gilead, Chiesi, Teva and Zambon; and fees for advisory boards from Vertex, Gilead, Chiesi and Menarini. SC has received honoraria for lectures from Vertex and Chiesi; and fees for advisory boards or consulting from Vertex and Profile Pharma.

KEYWORDS

Patient & public involvement; patient preference; treatment burden; discrete choice experiment; cystic fibrosis; CFTR modulators

ABBREVIATIONS

CF = cystic fibrosis; CFRD = cystic fibrosis related diabetes; DCE = discrete choice experiment; GORD = gastro-oesophageal reflux disease; HRQoL = health related quality of life; MNL = multinomial logit PERT = pancreatic enzyme replacement therapy; PwCF = people with cystic fibrosis

ABSTRACT

BACKGROUND: There is a growing consensus that the perspective of the patient should be considered in the evaluation of novel interventions.

RESEARCH QUESTION: What treatment outcomes matter to people with cystic fibrosis (CF), and what trade-offs would they make to realise these outcomes?

STUDY DESIGN AND METHODS: Adults attending a specialist CF centre were invited to complete an online discrete choice experiment (DCE). The DCE required participants to evaluate hypothetical CF treatment profiles, defined by impact on lung function, pulmonary exacerbations, abdominal symptoms, life expectancy, quality of life, inhaled medicines usage, and physiotherapy requirement. Choice data were analysed using multinomial logit and latent class models.

RESULTS: 103 people with CF completed the survey (median age 35 years (range 18-76); 52% female; mean ppFEV1 69% (SD 22)). On average, an improvement in life expectancy by 10 years or more had the greatest impact on treatment preference, followed by a 15% increase in lung function. However, it was shown that people would trade substantial reductions in these key outcomes to reduce treatment time or burden. Preference profiles were not uniform across the sample: three distinct subgroups were identified, each placing markedly different importance on the relative importance of both life expectancy and lung function compared to other attributes.

INTERPRETATION: The relative importance of treatment burden to people with CF, compared to life expectancy and lung function suggests it should be routinely captured in clinical trials as an important secondary outcome measure. When considering the patient perspective, it is important that decision makers recognise that the values of people with CF are not homogenous.

Cystic fibrosis (CF) is a rare genetic condition with an estimated live-birth incidence of between 1/2000 and 1/6000 in populations of European and Middle Eastern descent.[1] Most people with CF (PwCF) will require lifelong treatment involving frequent hospital visits and admissions and rigorous daily therapy regimens.

The average daily time associated with treatment has been estimated at over 1.5 hours.[2] This high level of treatment burden has a substantial impact on health-related quality of life (HRQoL), and is associated with reduced adherence.[3,4] PwCF have been shown to rationalise which treatments they take, depending on how they fit into their daily-life commitments,[2] with the lowest levels of adherence for treatments perceived to be more burdensome.[5,6] Low adherence commonly equates to poorer outcomes,[7,8] and has been associated with elevated costs for acute medical care,[9] and ultimately wasted medical resources.[10]

Recent surveys of CF communities have identified simplification of treatment burden as a key research priority.[11,12] The recent introduction of CFTR modulator therapies is transforming the outcomes and prognosis for many PwCF, with evidence emerging that their introduction is associated with reduced use of other treatments.[13] To date, however these innovations have been designed to be additive to existing regimens, so reduction of burden of treatment remains a priority.

Understanding how patients perceive and prioritise potentially competing outcomes is becoming increasingly important to the development and delivery of new CF therapies and regimens. A criticism of recent evaluations of new CF therapies is that current assessments of a drug's value either disregard or are insensitive to patient preferences, or the benefits they prioritise.[14] As the management of CF evolves, lower treatment burden is anticipated to become a cornerstone of the value that new CF therapies can bring to patients.[2,7] Currently, there is no agreed approach for technology assessments to objectively consider the values and priorities of patients,[15] although there is a growing consensus that such assessments should, in some systematic way, incorporate the patient perspective.[16,17]

This study sought to understand treatment preferences from the perspective of PwCF, the impact of treatment outcome on choice of treatment, and to quantify the trade-offs that people were willing to make between these outcomes. We focus on key clinical outcomes (lung function, life expectancy, and HRQoL), and known drivers of significant treatment burden (physiotherapy, inhaled medicines,

pulmonary exacerbation and pancreatic enzyme replacement therapy [PERT]). The primary objective of the research was to develop a set of metrics (marginal effects), that indicate the relative importance of different treatment outcomes for PwCF. We also include an exploratory analysis of how these preferences vary across the CF population.

Methods

This research formed part of VALU-CF, a cross-sectional study focused on the measurement and valuation of CF-specific HRQoL.[18] It uses a discrete choice experiment (DCE) to characterise the treatment preferences of PwCF. The DCE is a choice-based approach to eliciting preferences.[19] The approach enables researchers to estimate the relative importance of the characteristics, or 'attributes' of an intervention (e.g. dosing regimen, and efficacy of a drug). Each attribute may have a number of different 'levels' (dosing regimen for example might be daily, or twice daily). Examination of the relative preference for different levels within each attribute facilitates estimation of the trades offs that individuals are willing to accept between attributes. The theoretical basis underpinning DCEs is an assumption that individuals value interventions based on their component attributes,[20] and the likelihood of choosing one intervention over another is a function of the attributes of each intervention.[19,21] The attributes investigated in this study are the treatment outcome and burden impacts of a hypothetical new oral drug for CF.

Development of the DCE Survey

Development of the survey instrument followed good research practice guidelines for DCEs, and survey design.[22,23] The VALU-CF study and the DCE survey were approved by the NHS Health Research Authority (REC 19/YH/0423), and all participants provided informed consent.

The DCE presented each participant with 12 choice scenarios in which they were asked to choose between different hypothetical treatment options. An example choice scenario is shown in figure 1.

The treatment options were defined by seven attributes (table 1). All treatment options were described as once daily tablets with a very low risk of serious adverse events. The participant was asked to make a choice of adding one of the two treatments to their daily regimen, or opting out of the additional drug therapy. The 12 tasks were presented to each participant in a randomised order. The combination of treatment profiles presented in the choice scenarios were generated using Ngene software (Choice Metrics), employing a D-efficient design, (further experimental design details in e-Appendix 1).

Key treatment outcome attributes to be considered were first identified by expert opinion, and through the literature. The attribute list was refined and finalised based on feedback from a focus group with PwCF, and carers of PwCF, conducted in June 2019. The design included seven attributes that considered the impact of a hypothetical new treatment on: lung function (change in $ppFEV_1$); life expectancy; frequency of pulmonary exacerbations (change in number of days on IV antibiotics); gastrointestinal symptoms and the need for PERT; overall quality of life; time spent on inhaled medicines; and time spent on physiotherapy. The levels of the attributes (informed by evidence, consultation with clinical and outcomes experts and PwCF), were chosen to represent feasible and clinically meaningful outcomes of hypothetical new treatments analogous to triple combination CFTR modulator therapy.[24]

The survey also contained predominantly closed questions on demographics, HRQoL (EQ-5D-5L and self-rated health visual analogue scale [VAS]), treatment complexity [e-Appendix 2, e-Table 1],[25] and treatment burden, reported elsewhere.[26] It was estimated that survey completion would take 20-25 minutes.

Table 1 Attributes and levels

Attribute	Level
Effect on lung function (percent predicted FEV1)	1. No change 2. A modest deterioration (5% decrease in ppFEV1) 3. A modest improvement (5% increase in ppFEV1) 4. An excellent improvement (15% increase in ppFEV1)
Effect on need for IV antibiotic treatment of exacerbations	1. No change in number of IV antibiotics courses needed each year 2. About half the number of IV courses compared to current treatment
Effect on abdominal symptoms (appetite, abdominal pain, constipation, and nausea)	1. No change in symptoms 2. Improvement in symptoms

	3.	Improvement in symptoms and a reduction in the number of pancreatic enzymes needed
Effect on average life expectancies	1. 2. 3. 4.	No change to current life expectancy Life expectancy increases by 5 years Life expectancy increases by 10 years Life expectancy increases by 15 years
Effect on overall quality of life	1. 2. 3.	No change in overall quality of life Good improvement in overall quality of life (e.g. an improvement of 10%) Excellent improvement in overall quality of life (e.g. an improvement of 20%)
Impact on use of inhaled medicines	1. 2. 3.	No impact on time currently spent on inhaled treatments A modest (25%) reduction in time spent on inhaled treatments A large (50%) reduction in time spent on inhaled treatments
Impact on current physio regimen/ airways clearance therapy (ACT)	1. 2. 3.	No impact on the time currently spent on physio Time spent on physio is halved Able to fully stop physio

Recruitment and Data Collection

Administered online and hosted by SurveyEngine (Germany), the survey ran between July and October 2020. Adopting a purposive sampling approach, 276 adults with CF attending the Royal Brompton Hospital Adult CF Centre were emailed an invitation to participate. Inclusion criteria required the participants to have a CF diagnosis, be over the age of 18 years, and have the mental capacity to complete the survey. Inpatients experiencing acute exacerbations and judged by the research nurse to be too unwell to be approached were excluded. A £10 online voucher was offered as an incentive to participate, and respondents were sent up to two reminder emails. The survey was preceded by an electronic participant information sheet and an informed consent section that included optional linkage of survey data to the participant's UK CF Registry data.

The survey was paused after 13 completions in an initial 'pilot' phase. Based on feedback, minor formatting changes were made to the display of the attributes to highlight the elements of the attributes that changed across choice sets, and the direction of that change.

Statistical Analysis

All analyses were conducted using Stata IC (StataCorp). Incomplete surveys were omitted from the analysis.

The DCE data were analysed initially with a multinomial logit (MNL) model. The model included a constant to represent the choice of declining either treatment in each choice scenario. In the base case model (MNL Model 1), all attribute variables were dummy coded, however, to simplify trade-off

calculations a model (MNL Model 2), with the lung function and life expectancy attributes coded as continuous variables was also estimated.

Trade-offs were estimated against both lung function and life expectancy by calculating the ratios of their marginal effects to those of other attributes to provide the marginal rate of substitution per unit change in ppFEV1 or life expectancy. Trade-off confidence intervals were estimated using the delta method.[27]

A simplifying assumption of the MNL model is that preferences are uniform across the sample. To address this limitation, a latent class (LC) model was estimated using lclogit2, a user-written Stata program.[28] LC models extend the MNL by incorporating unobserved heterogeneity of preferences across participants. The LC model assumes a discrete number of classes of preference profile within the population, whose membership is characterised by unobserved variables.[28,29] Final model specification was guided by minimisation of the Bayesian Information Criterion (BIC). Probability of class membership was estimated for each participant and used to designate specific classes..

Methods for scoring and detailed analysis of the treatment burden measures in this study (including their relative performance), are published separately.[26] The cross-walk algorithm was used to score the EQ-5D-5L measure.[30]

Results

Survey Population

The survey was completed by 103 pwCF giving a response rate was 37%. All participants consented for their registry data to be linked with the survey, however an error in participant tracking meant that we were unable to identify and link the data of two participants. The choice data for these two participants were retained in the DCE modelling. Five patients were excluded from recruitment, (three for mental health reasons, two because they were new to the service), no patients were excluded due to severity of CF.

The survey sample (table 2), 52% female with a median age of 35 years (range 18-76 years), and a ppFEV1 of 69% (SD 22), showed no differences to the centre's CF population with regards to lung function, BMI, or use of mucolytics or osmotic therapies (e-Table 2).[31] The sample was also broadly representative of the UK adult CF population against key clinical and treatment characteristics.[31] Mean scores for HRQoL (EQ-5D-5L index: 0.77), and treatment burden (CFQ-R treatment burden domain: 54), were similar to those for patients with mild disease in a recent study by Acaster *et al.*[32] On average, the sample spent 92 minutes managing a total of 14 treatments each day.

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206 **Table 2** Characteristics of survey participants

	Sample number	Mean (SD) or number (%)	Median (IQR)
Demographics			
Age (years)	101	36 (11)	35 (17)
Gender (female)	101	52 (52%)	
Clinical measures			
BMI	101	23 (3.2)	23 (3.6)
ppFEV1	101	69 (22)	69 (30)
Mild (>70%)[a]	101	50 (50%)	
Moderate (40-70%)		39 (39%)	
Severe (<40%)		12 (12%)	
absFEV1 (l)	99	2.5 (1.1)	2.3 (1.4)
ppFVC	94	85 (20)	87 (27)
Absolute FVC (l)	94	3.7 (1.1)	3.6 (1.5)
Diagnosis of GORD	101	42 (42%)	
Diagnosis of CFRD	101	29 (29%)	
Treatment characteristics			
Treatment complexity score	101	22 (7.4)	23 (9)
Total treatment time (mins/day)	103	92 (71)	85 (65)
Physiotherapy time (mins/day)	103	38 (33)	30 (40)
Inhaled medicines time (mins/day)	103	43 (38)	30 (40)
No. chronic treatments	101	13 (4.8)	13 (5)
Prescribed CFTR modulator	101	65 (65%)	
ivacaftor	101	4 (4%)	
tezacaftor/ivacaftor		29 (29%)	
elexacaftor/tezacaftor/ivacaftor		33 (33%)	
Received IV antibiotics in last year	101	36 (36%)	
Number of IV antibiotic courses in last year[b]	36	2.6 (2.1)	2 (3)
HRQoL and treatment burden measures			
EQ-5D Index score	103	0.77 (0.19)	0.77 (0.2)
EQ-5D VAS score	103	75 (16)	80 (22)
CFQ-R treatment burden domain score	103	54 (23)	56 (33)
CFQoL treatment burden domain score	103	64 (26)	67 (40)

[a]Percentages do not sum to 100 due to rounding

[b]For those who received at least one IV antibiotic course

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208 *Outcome Preferences*

209 The 103 participants, each with 12 choice scenarios generated 1236 observations for analysis. All

210 responses were included in the analysis.[33] Participants chose not to take up either treatment for a

211 total of 73 (6%) of the choice scenarios, with 1(1%) participant opting out of treatment in all 12

choice scenarios. One participant selected option B for all scenarios which might suggest task non-attendance.

Multinomial Logit Model Results

The MNL model estimates coefficients that may be interpreted as mean marginal effects for treatment outcomes. These results (MNL Model 1) are presented in table 3 and figure 2.

Table 3 MNL Model 1 results.

Attribute	Parameter (level)	Marginal effect	95% CI
	Opt-out constant	0.4	-0.35, 1.16
Lung function	modest deterioration (-5%)	-0.45**	-0.79, -0.11
	no change	referent	
	modest improvement (+5%)	0.65***	0.36, 0.95
	excellent improvement (+15%)	1.24***	0.77, 1.72
Need for IV antibiotics	no change	referent	
	half the number of IV courses	0.27**	0.1, 0.44
Abdominal symptoms	no change	referent	
	improvement in symptoms	0.26**	0.02, 0.51
	improvement in symptoms and a reduction in pancreatic enzymes	0.37***	0.17, 0.58
Life expectancy	no change	referent	
	increases by 5 years	0.55***	0.27, 0.82
	increases by 10 years	1.85***	1.45, 2.26
	increases by 15 years	2.34***	1.83, 2.85
Overall quality of life	no change	referent	
	good improvement (+10%)	0.31**	0.12, 0.5
	excellent improvement (+20%)	0.65***	0.43, 0.88
Use of inhaled medicines	no change	referent	
	a modest reduction in time spent (-25%)	0.18**	0.01, 0.35
	a large reduction in time spent (-50%)	0.3**	0.11, 0.48
Physio/ ACT	no change	referent	
	time spent on physio is halved	0.19**	0.07, 0.32
	able to fully stop physio	0.51***	0.26, 0.75
Model statistics	No. Observations: 1236; McFadden's R^2: 0.32; LL: -924; AIC: 1882; BIC: 1988		

LL: log likelihood; AIC: Akaike information criteria; BIC: Bayesian information criteria
* *P* <0.1 ** *P* <0.05 *** *P* <0.001

The non-significant opt-out coefficient indicated no propensity for participants to opt-out of treatment. Marginal effects for all attributes were significantly different to zero and positive (with the exception of a 5% reduction of ppFEV1 which was negative, as expected) and increase in magnitude in a logically consistent manner. People showed preference for improvements in life

expectancy of 10 years or more over all other attributes. Improvement in lung function also had a notable impact on choice of treatment. When considering treatment burden-related attributes, the greatest preference was shown for stopping physiotherapy, followed by reduced PERT, coupled with improved abdominal symptoms.

Table 4 summarises willingness to accept a reduction in lung function or additional life expectancy for an improvement in other outcomes (based on MNL Model 2, e-Table 3). The largest trade-offs were for an "excellent improvement in quality of life", with people prepared to accept a reduction of 8.2 ppFEV1 (95% CI 5.8 to 10.7), or 4.2 years additional life expectancy (95% CI 3.1 to 5.4) on average. People were also prepared to accept notable reductions in lung function or additional life expectancy to reduce their treatment burden: 6.1 ppFEV1 (95% CI 3.6 to 8.7) or 3.2 years additional life expectancy (1.8 to 4.5) to fully stop physio; 5.3 ppFEV1 (3.3 to 7.3) or 2.7 years additional life expectancy (1.6 to 2.8) if abdominal symptoms improved with a concomitant reduction of PERT; and 4.4 ppFEV1 (2.6 to 6.3) or 2.3 years additional life expectancy (1.3 to 3.3) to halve the time spent on inhaled medicines.

Table 4 Willingness to accept a reduction in ppFEV1 or additional life expectancy against other treatment outcomes.

Attribute	Acceptable reduction in ppFEV1 (95% CI)	Acceptable reduction additional life expectancy[a] (95% CI)
Excellent improvement (+20%) in QoL	8.2 (5.8 to 10.7)	4.2 (3.1 to 5.4)
Able to fully stop physio	6.1 (3.6 to 8.7)	3.2 (1.8 to 4.5)
Abdominal symptoms improved and enzymes reduced	5.3 (3.3 to 7.3)	2.7 (1.6 to 3.8)
A large reduction in time spent (-50%) on inhaled medicines	4.4 (2.6 to 6.3)	2.3 (1.3 to 3.3)
Abdominal symptoms improved	4.2 (1.7 to 6.8)	2.2 (0.8 to 3.5)
Good improvement (+10%) in QoL	3.5 (1.2 to 5.8)	1.8 (0.7 to 2.9)
Time spent on physio is halved	2.7 (1.2 to 4.3)	1.4 (0.6 to 2.2)
IV days halved	2.4 (0.7 to 4.1)	1.2 (0.3 to 2.2)
Per year increase in life expectancy	1.9 (1.5 to 2.4)	-
A modest reduction in time spent (-25%) on inhaled medicines	1.9 (0.0 to 3.8)	1.0 (0.0 to 2.0)
Per 1% increase in predicted FEV1	-	0.5 (0.4 to 0.6)

[a] Additional life expectancy should be interpreted as the additional life expectancy conferred by the hypothetical treatments presented in the DCE, beyond existing life expectancy

In secondary analyses, we investigated the impact on preferences of having a CFTR modulator prescription (e-Figure 1, e-Table 4), and of responding to the survey after it was announced that elexacaftor-tezacaftor-ivacaftor (ETI) would be reimbursed in the UK (e-Figure 2). No significant differences in preferences were found for those who completed the survey prior to ETI reimbursement compared to those who completed after its general availability. Those not

prescribed CFTR modulators tended to be less concerned about modest reductions in lung function, and value more highly improvements in abdominal symptoms as well as significant quality of life improvements. Consequently this group were prepare to accept larger reductions in lung function in order to improve their abdominal symptoms. Those not prescribed CFTR modulators tended to have a lower treatment burden than those on modulators, but no other significant differences in clinical or demographic characteristics were observed (e-Table 5).

Latent Class Model Results

A model with three latent classes was deemed to be both the best fit, and the most logically coherent model. Based on probability of class membership, the model predicted that 43% of the sample fell into Class 1, 47% in Class 2, and 10% in Class 3.

The results of the latent class model are shown in table 5 and figure 3. Consistent with the MNL model, improvements in life expectancy were overall the strongest drivers of preference, however the strength of this preference relative to other attributes differs markedly across the classes. Class 1 is primarily characterised by improvements in life expectancy. They were indifferent to a modest reduction in lung function, and to reductions in most treatment burden-related and abdominal symptom outcomes. However, a 50% reduction of time spent on inhaled medicines was viewed as equivalent to a modest (5%) improvement in lung function or a 20% improvement in quality of life. Conversely, Class 2 strongly valued an increase in lung function and was inclined to avoid a decrease in lung function, and reduce treatment burden, with stopping physiotherapy the preferred treatment burden outcome. Owing to the small sample membership for Class 3, preferences should be interpreted with caution, however this class had a stronger likelihood of opting out of an additional treatment and appeared indifferent to changes in lung function.

273 **Table 5** Latent class model results.

Attribute	Parameter (Level)	**Class 1** [a] Share p=0.43 [b]		**Class 2** Share p=0.47		**Class 3** Share p=0.10	
		Marginal effect	95% CI	Marginal effect	95% CI	Marginal effect	95% CI
	Opt-out constant	0.58	-0.81, 1.98	-0.72	-1.7, 0.25	4.30***	2.16, 6.44
Lung function	modest deterioration (-5%)	-0.11	-0.98, 0.75	-1.11***	-1.64, -0.57	-0.92	-1.91, 0.06
	no change	referent					
	modest improvement (+5%)	0.97*	0.11, 1.83	0.97***	0.6, 1.35	0.2	-0.78, 1.19
	excellent improvement (+15%)	1.85**	0.7, 3	1.73***	1.16, 2.31	0.83	-0.35, 2.01
Need for IV antibiotics	no change	referent					
	half the number of IV courses	0.27	-0.24, 0.78	0.52***	0.27, 0.77	-0.21	-0.83, 0.42
Abdominal symptoms	no change	referent					
	improvement in symptoms	-0.09	-0.68, 0.5	0.57**	0.23, 0.91	0.17	-0.58, 0.93
	improvement in symptoms and a reduction in pancreatic enzymes	0.21	-0.35, 0.77	0.67***	0.32, 1.02	0.34	-0.47, 1.15
Life expectancy	no change	referent					
	increases by 5 years	1.85***	0.94, 2.75	0.49	-0.02, 1.01	1.79**	0.45, 3.12
	increases by 10 years	4.79***	3.57, 6.02	1.49***	0.96, 2.01	2.45**	1.04, 3.86
	increases by 15 years	6.62***	5.08, 8.16	1.71***	1.1, 2.32	3.05***	1.51, 4.59
Overall quality of life	no change	referent					
	good improvement (+10%)	0.89***	0.37, 1.42	0.29	0, 0.58	0.46	-0.35, 1.27
	excellent improvement (20%)	1.14***	0.57, 1.71	0.9***	0.56, 1.25	0.72	-0.08, 1.52
Use of inhaled medicines	no change	referent					
	a modest reduction in time spent (25%)	0.24	-0.37, 0.85	0.20	-0.11, 0.5	1.13**	0.29, 1.97
	a large reduction in time spent (50%)	0.95**	0.41, 1.49	0.34**	0.03, 0.65	0.99**	0.08, 1.9
Physio/ ACT	no change	referent					
	time spent on physio is halved	0.53**	0.02, 1.04	0.17	-0.1, 0.45	0.45	-0.32, 1.22
	able to fully stop physio	0.71	-0.17, 1.59	0.80***	0.47, 1.13	0.91**	0.08, 1.74
Model statistics	No. Observations: 3708; McFadden's R^2: n/a; LL: -697; AIC: 1501; BIC: 1831						
	* P <0.1 ** P <0.05 *** P <0.001						

[a] As marginal effects are calculated relative to the reference level for each class, they are not directly comparable across classes, the ratios between effects however may be directly compared.

[b] Probability of class membership, equates to percentage class share of the population

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Characteristics of the predicted classes are summarised in table 6. Whilst some significant predictors of class membership were observed, few of the *a priori* specified participant characteristics were found to be strong predictors of class membership. There were statistically significant differences in lung function between participants who were likely to belong to Class 1 and Class 2 (absolute FEV1, *P*= 0.03; absolute FVC, *P*= 0.01). Nominally, Class 2 had an increased likelihood of a CFRD diagnosis, longer overall treatment time, lower HRQoL than Class 1. There were no differences between Class 1 and Class 2 in terms of age, gender or treatment burden or complexity scores. Compared to Class 1, Class 3 were more likely to be female (*P*=0.06), had a lower treatment complexity score (p=0.01), and lower treatment burden as measured by the CFQ-R (*P*=0.03). Nominally, Class 3 spent less time on all forms of treatment, were less likely to receive IV antibiotics and had a superior HRQoL compared to both Classes 1 and 2.

288 **Table 6** Comparison of predicted class member characteristics

	Class 1 N=45	Class 2 N=48	Class 3 N=10	*P* [a]
Demographics				
Age (years)	36	36	36	0.99
Gender (% female)	43	54	78*	0.1
Clinical measures				
ppFEV1	71	64	85*	0.02
Mild (%)	52	43	70	0.4
Moderate (%)	36	43	30	
Severe (%)	11	15	0	
absFEV1 (l)	2.72	2.22**	2.51	0.08
ppFVC	88	80*	99	0.01
absFVC (l)	3.94	3.35**	3.88	0.04
Diagnosis of GERD (%)	41	42	44	0.98
Diagnosis of CFRD (%)	25	33	22	0.6
BMI	23	23	24	0.7
Treatment characteristics				
Treatment complexity score	22	23	16**	0.01
Total treatment time (mins/day)	91	104	42**	0.04
Physiotherapy time (mins/day)	38	42	17*	0.09
Inhaled medicines time (mins/day)	45	46	19*	0.1
No. chronic treatments	13	14	9**	0.02
Prescribed CFTR modulator (%)	70	60	67	0.6
Prescribed elexacaftor/tezacaftor/ivacaftor (%)	34	29	44	0.7
Received IV antibiotics in last year (%)	39	35	22	0.6
Number of IV antibiotic courses in last year [b]	2.5	2.9	1.5	0.6
HRQoL and treatment burden measures				
EQ-5D Index score	0.80	0.72**	0.88*	0.02
EQ-5D VAS score	75	74	80	0.6
CFQ-R treatment burden domain score	54	50	74**	0.007
CFQoL treatment burden domain score	63	63	76	0.3
MTBQ index score (reversed)	80	81	90**	0.09

* P <0.1 ** P <0.05 t-test comparisons against Class 1

[a] One-way ANOVA tests used for continuous variables, Pearson's X^2 used for categorical variables

[b] For those who received at least one IV antibiotic course

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290 Discussion

291 In 2018 a survey of PwCF identified treatment burden as their number one priority research topic.[11]

292 The improved prognosis that many PwCF can expect as a consequence of more effective therapies is

likely to reinforce this priority. To our knowledge, this is the first study explicitly quantify the relative importance to PwCF of reducing diverse aspects of treatment burden related to the management of CF.

As would be expected for a life-limiting chronic respiratory condition, PwCF placed greatest importance on treatments that will extend life expectancy; improvements to lung function are also very important. However, the extent to which people are willing to trade gains in these two major outcomes to reduce their treatment burden or, for example reduce their abdominal symptoms underscores the relative importance to the patient of these aspects of their disease and its management. Of the treatment-burden related outcomes, people were prepared to accept the largest reductions to stop physiotherapy, followed by reducing PERT, coupled with an improvement in GI symptoms, and halving of inhaled medicines. The findings are in broad agreement with a recent study suggesting that airways clearance therapy, nebulised antibiotics and PERT are the top 3 most burdensome CF treatments.[34] The trade-offs reported may be additive (assuming no interactions or dependencies between attributes), suggesting for example that people may be willing to accept a reduction in lung function of over 5% predicted FEV1 for a new treatment that conferred a 50% reduction in both IV days and time spent on physiotherapy. An investigation of the impact of CFTR modulator prescription on preferences suggests that those not prescribed modulators place greater importance on reducing abdominal symptoms than those who are. This finding aligns with emerging evidence that the modulators improve digestive outcomes in CF,[35] and may suggest that following initiation on a CFTR modulator, these symptoms become less of a priority for the patient.

A secondary objective of the research was to explore how treatment preferences vary across the CF population; in the latent class model, we identified three distinct subgroups with respect to outcome preferences. Differences across the preference profiles were marked: Class 1 prioritise life expectancy over all other outcomes and appear to be indifferent to most treatment burden outcomes, whereas people in Class 2 prioritised preservation or improvement in lung function and in treatment burden reduction. Class 3 tended to have better overall health, which likely explains their tendency not to opt for an additional treatment in the experiment, however interpretation of membership characteristics for Class 3 should be cautious owing to its small size. There was a slight nominal trend for better overall health, HRQoL and objective treatment burden in Class 1 versus Class 2, however these were found to be poor predictors of class membership. While the study was not designed or powered to address the question of population heterogeneity, our working hypothesis is that these differences in preference may be better explained by attitudinal, rather than clinical characteristics.

This study may be prone to potential biases and limitations. As with all surveys there is a risk of response bias, for example through answering strategically to influence policy.[36] To mitigate this, the survey was designed following general good survey practice guidelines.[23] Further, the broad agreement in relative importance of various aspects of treatment burden items of our findings with other recent studies suggests that any such bias is limited.[11,34] Although a good response rate of 37% for an on-line questionnaire, there may still be a non-response bias. However, there is a growing body of evidence suggesting little to no relationship between response rate and non-response bias.[37] The use of a purposive, rather than a random sampling approach poses a risk of selection bias, though in terms of clinical and demographic characteristics, the sample is broadly representative of the of the population of adults with CF in the UK, with similar mean age, ppFEV and BMI.[38] The co-incidental UK reimbursement decision for ETI during the study period may have introduced chronological bias, although no differences in preferences for the pre-and post-launch segments of the sample were noted. DCEs focus on the stated preferences of participants in hypothetical scenarios; these may not truly reflect the choices that might be made in real life. Research into the external validity of DCEs is limited, although a recent meta-analysis suggested well designed experiments can predict choice reasonably well.[36,39] While we were unable to compare the stated preference results of this study with revealed preferences from the real world, it is our expectation that engagement of PwCF throughout the conceptualisation, design, and piloting of the study has enhanced its external validity.

The study was designed with a sample sufficient to investigate main effects model, which assumes no interaction between attributes. Similarly, the study was not designed to assess preference heterogeneity in the primary analysis; the latent class results should therefore be interpreted as indicative.

As a single centre study, the generalizability of the findings presented to other settings here may be limited. However, the sample was similar to the overall UK CF population against key clinical and demographic parameters,[38] and scores for health state utility (mean 0.77), and treatment burden measured by the CFQ-R (mean 54), were similar to those reported elsewhere for mild patients (ppFEV1 ≥ 70).[32] At the time of the study, there was limited patient experience with ETI. Given ETI's documented impact on treatment burden,[13,40] the preferences presented in this study may be subject to change now that the eligible CF population is established on the treatment.

Interpretation

The findings of this study add substantially to a very sparse literature on the preferences of PwCF, and suggest that on average, they would trade benefits likely to be captured in conventional trials

(ppFEV1) and economic evaluations (HRQoL, life expectancy), for benefits that might not be captured within current conventional evaluations (e.g. reduced treatment burden and time). Further, our results indicate that PwCF are not a homogeneous group with regard to the outcomes they prioritise: this has important equity implications when considering how patient values should inform decision making, both on the ground at the clinic, and at the health-system level. The study provides important evidence on the relative importance of outcomes from a patient perspective, that could be used alongside other scientific evidence in health technology appraisals to support decision-making for either the regulation or funding of CF treatments. Moreover, the comparative importance of treatment burden for patients suggests it should be considered as an important secondary outcome in CF when designing future prospective trials of novel therapies.

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CONTRIBUTORS

RC had full access to all the study data and takes responsibility for the integrity of the data, analysis and manuscript content. The study was conceived by SC, JW, NS and JA. All authors were involved in study planning and design. SC, JM, DO and RC were involved in study delivery. RC prepared the data and carried out statistical analysis. SC, JA, NS, and MR provided expert opinion on development of the analysis and interpreting the data. RC developed and wrote the manuscript, with critical revisions and review of the final manuscript from all other authors.

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Take-home points

Study Question: What treatment outcomes matter to people with cystic fibrosis, and what trade-offs would they make to realise these outcomes?

Results: Improving life expectancy was found to be the most important outcome in this study, but people with cystic fibrosis were prepared to accept substantial reductions in this outcome, and in lung function to reduce their treatment burden.

Interpretation: Awareness of the priorities of people with cystic fibrosis with regards to their treatment outcomes may improve decision making both at the policy and at the clinic levels.

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Legends To The Figures

Figure 1

An example choice scenario from the survey.

Figure 2

MNL Model 1 results. Values are mean marginal effect, ± 95% CI. The marginal effect for no change (reference level) is represented by the dashed horizontal line. Abd. sympt, abdominal symptoms; LE, life expectancy (years); QoL, overall quality of life; Inh. meds, inhaled medications; Physio, physiotherapy; impr, symptoms improved; impr. enzymes reduced, symptoms reduced and pancreatic enzymes reduced.

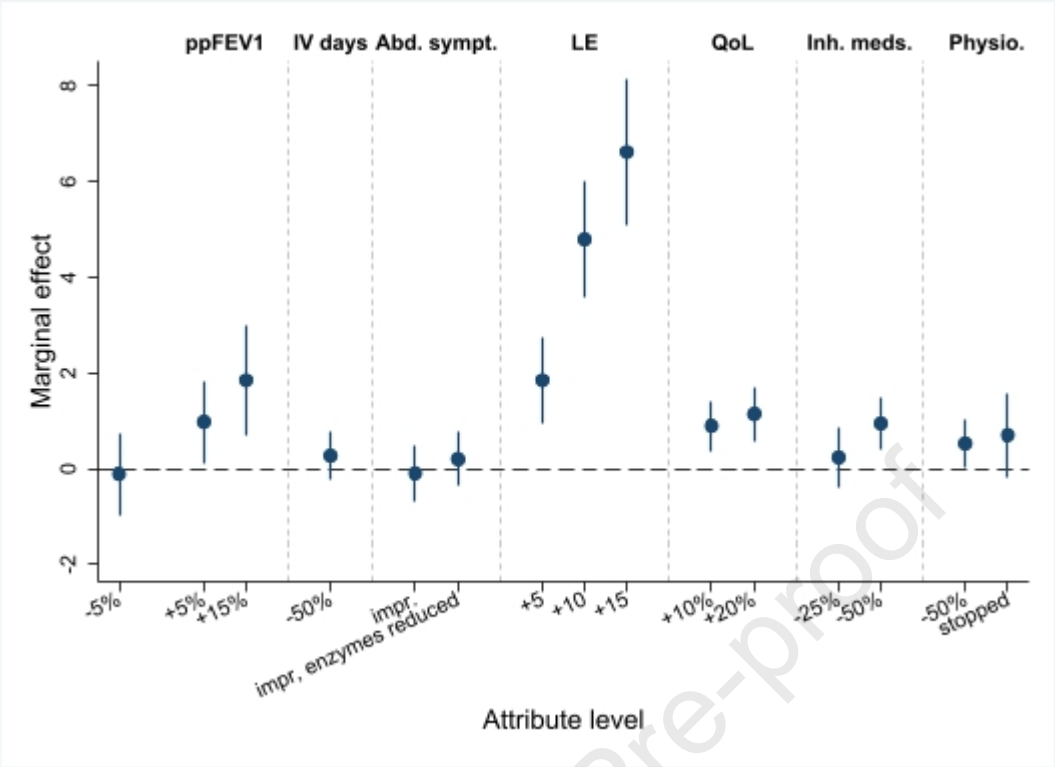
Figure 3

Latent Class model results for (A) Class 1, (B) Class 2, and (C) Class 3. Values are mean marginal effect, ± 95% CI. The marginal effect for no change (reference level) is represented by the dashed horizontal line. Abd. sympt, abdominal symptoms; LE, life expectancy (years); QoL, overall quality of life; Inh. meds, inhaled medications; Physio, physiotherapy; impr, symptoms improved; impr. enzymes reduced, symptoms reduced and pancreatic enzymes reduced.

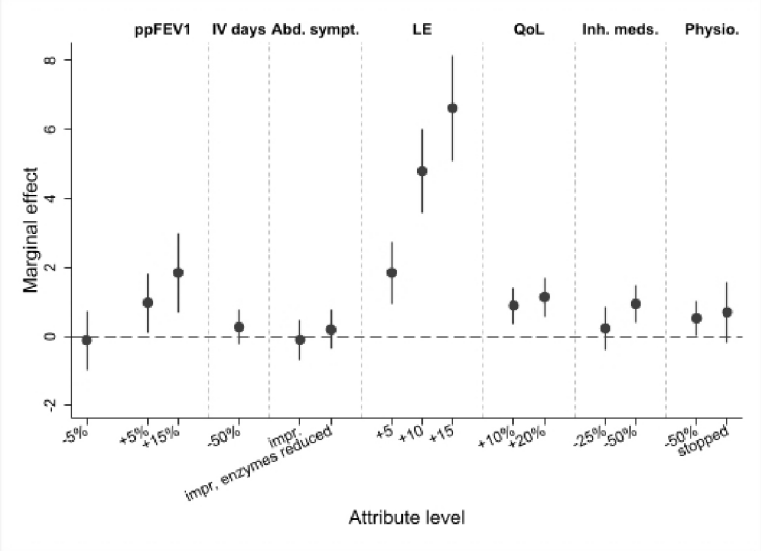
Please carefully review the two hypothetical CF treatment profiles below:

If both of these treatments were available to you this year, and you were offered a choice of adding one of these to your current treatment regimen, or remaining on just your current treatment, what would you choose to do:

	Treatment A		Treatment B		Neither
Effect on lung function (percent predicted FEV1)	A **modest deterioration** (5% decrease in ppFEV1)		An **excellent improvement** (15% increase in ppFEV1)		I would choose **neither** and remain on my current **treatment** regimen
Effect on need for IV antibiotic treatment of exacerbations	**No change** in number of IV antibiotics courses needed each year		About half the number of IV courses compared to current treatment (e.g. a patient who has two 14 day courses a year of IV antibiotics would expect one 14 day course a year with this treatment)		
Effect on abdominal symptoms (appetite, abdominal pain, constipation, and nausea)	Improvement in symptoms and a reduction in the number of pancreatic enzymes needed		**No change** in symptoms		
Effect on average life expectancies	Life expectancy increases by 10 years		**No change** to current life expectancy		
Effect on overall quality of life	**No change** in overall quality of life		Good improvement in overall quality of life (e.g. an improvement of 10%)		
Impact on use of inhaled medicines	**No impact** on time currently spent on inhaled treatments		A large (50%) reduction in time spent on inhaled treatments (e.g. a patient who currently spends 60 mins a day, would now spend 30 mins)		
Impact on current phyisio regimen/ airways clearance therapy (ACT)	Able to fully stop physio		Time spent on physio is halved		
Which would you choose?	○		○		○



A



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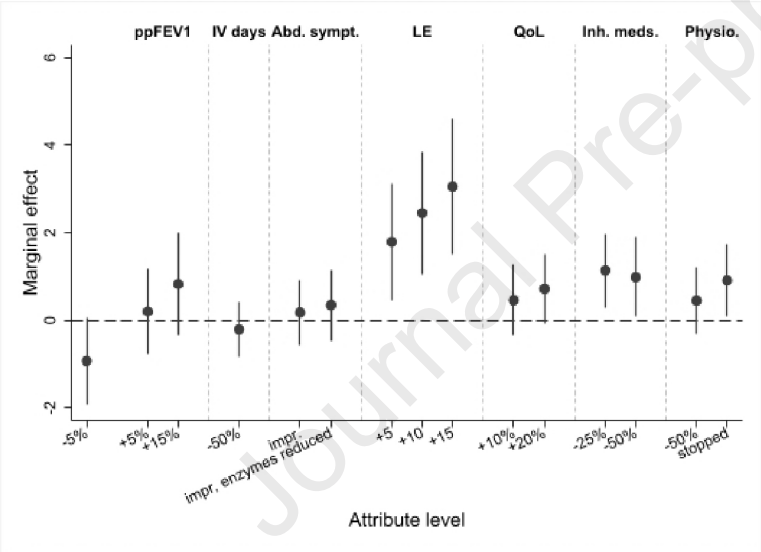

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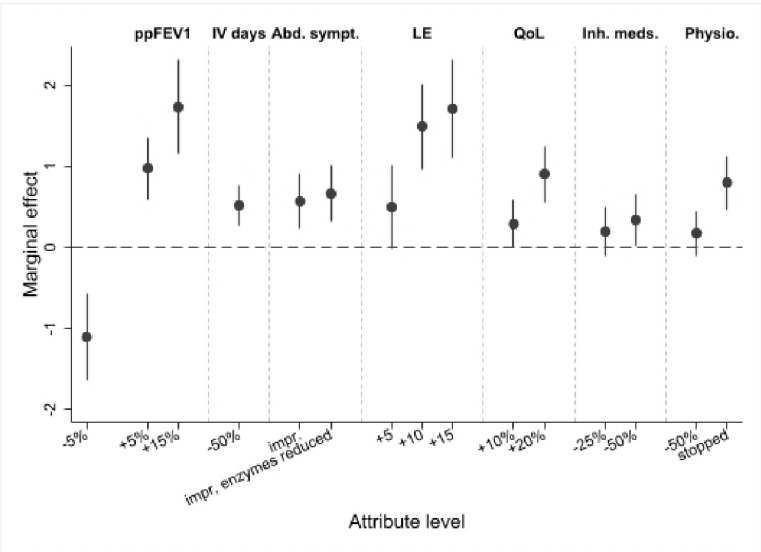

SUPPLEMENTARY FILE

e-Appendix 1:

Experimental Design

Efficient designs facilitate model estimation with smaller sample sizes than alternative experimental design methods.[1] The design assumed that the primary model would be a multinomial logit model (MNL), estimating main effects with dummy coded variables. Initially, the prior parameters for the design were set at near-0 positive values for all parameters except the lung function attribute level that indicated a 5% decrease in $ppFEV_1$, which was assumed to be negative. After 35 participants had completed the survey, a multinomial logit (MNL) model was estimated, and its coefficients used to provide Bayesian priors for an updated experimental design. The generated design comprised 36 choice pairs, grouped into 3 blocks, with each participant randomly assigned to one of the three blocks of 12 choice scenarios.

e-Appendix 2:

Treatment Complexity Score

The treatment complexity score (TCS) was developed by Sawicki *et al.*[2] as a means to quantify the effort involved in using CF medications, based on their frequency, administration time, and method. Each treatment is assigned a complexity of 1 (low complexity), 2, or 3 (high complexity). Scores for each treatment are summed to give an overall TCS for each participant. High TCS score suggests high treatment complexity. TCS scoring in this study was based on the original, although with some modification,[3] to add treatments that were not in the original (Table e1)

1. Bliemer MCJ, Rose JM. Efficiency and Sample Size Requirements for Stated Choice Studies. In:2005.
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e-Table 1

The modified version of Sawicki *et al*.'s treatment complexity score table

TCS Score = 1 point	TCS Score = 2 points	TCS Score = 3 points
Acid blockers	Antibiotics (nebulized OD)	Antifungals (inhaled) *
Analgesics	DNase (OD / OR)	Antibiotics (nebulized (BD/TDS)
Angiotensin receptor agonists *	Hypertonic saline (OD)	DNase (BD) *
Antibiotics (inhaled DPI) *	Pancreatic enzymes	Hypertonic saline (BD) *
Anticoagulants *	CFTR modulator *	Mannitol (DPI)
Antidepressants		Insulin
Antiemetics *		Colistin (nebulized) *
Antiepileptic *		Oxygen
Antifungals (oral) *		Airway clearance
Antihistamines *		Noninvasive ventilation *
Anti-inflammatories *		
Antiviral *		
Beta blocker *		
Bisphosphonates *		
Bronchodilators (inhaled)		
Bronchodilators (oral)		
Chronic oral antibiotics		
Corticosteroids (inhaled)		
Corticosteroids (inhaled) + LABA		
Corticosteroids (oral)		
Diuretics		
Immunosuppressants (oral) *		
Tranexamic acid 1 gm (TDS, PRN) *		
Metformin *		
Migraine prophylaxis *		
Minerals (oral)		
Nasal rinse/ spray *		
Prophylactic antibiotics (oral)		
Ropinirole *		
Statin *		
Tamoxifen *		
Vitamins (oral)		
Gastrointestinal medicines *		

* The newly added treatments to Sawicki et al.'s original version – none of the assigned treatments from the original version were moved to different categories or removed from the scale.

Abbreviations: TCS = treatment complexity score, DPI = dry powder inhaler, LABA = long-acting beta agonist, TDS = three times a day, PRN = as required, OD = once a day, OR = other regimen, BD = twice a day.

e-Table 2

Comparison of characteristics of participants with those of Royal Brompton Hospital Adult CF Centre

	Survey Sample N=101	RBH Adult CF Centre N=550
Clinical measures		
ppFEV1		
Unadjusted mean	69.5	67.0
Median	69.2	68
BMI		
Unadjusted mean	22.8	23.0
Median	22.5	22.5
Treatment characteristics		
Prescribed DNase	91%	90.9%
Prescribed hypertonic saline / mannitol	60%	56.0%

e-Table 3

MNL Model 2 with continuous variables for lung function & life expectancy

Attribute	Parameter (level)	Marginal effect	95% CI
Opt-out	-	0.44	-0.21, 1.09
Lung function	per 1% change in lung function	0.08***	0.06, 0.11
Need for IV antibiotics	no change	referent	
	half the number of IV courses	0.2**	0.04, 0.36
Abdominal symptoms	no change	referent	
	improvement in symptoms	0.35**	0.12, 0.59
	improvement in symptoms and a reduction in pancreatic enzymes	0.44***	0.25, 0.63
Life expectancy	per 1 year increase in life expectancy	0.16***	0.13, 0.20
Overall quality of life	no change	referent	
	good improvement (+10%)	0.29**	0.10, 0.48
	excellent improvement (+20%)	0.69***	0.47, 0.91
Use of inhaled medicines	no change	referent	
	a modest reduction in time spent (-25%)	0.16*	0.00, 0.32
	a large reduction in time spent (-50%)	0.37***	0.20, 0.54
Physio/ ACT	no change	referent	
	time spent on physio is halved	0.23***	0.11, 0.35
	able to fully stop physio	0.51***	0.27, 0.75
Model statistics	No. Observations: 1236; McFadden's R^2: 0.31; LL: -933; AIC: 1892; BIC: 1973		

LL: log likelihood; AIC: Akaike information criteria; BIC: Bayesian information criteria

*** *P* <0.1 ** p<0.05 *** p<0.001**

e-Table 4

Willingness to accept a reduction in ppFEV1 or additional life expectancy against other treatment outcomes, for those prescribed or not prescribed CFTR modulators

Attribute	Acceptable reduction in ppFEV1 (95% CI)		Acceptable reduction additional life expectancy[a] (95% CI)	
	Prescribed CFTR N=66	Not prescribed CFTR N=35	Prescribed CFTR N=66	Not prescribed CFTR N=35
Excellent improvement (+20%) in QoL	6.5 (3.7 to 9.2)	11.4 (6.1 to 16.6)	3.4 (2.1 to 4.6)	5.8 (3.4 to 8.3)
Able to fully stop physio	6.3 (2.8 to 9.8)	5.9 (2.2 to 9.6)	3.3 (1.5 to 5.1)	3.1 (1.0 to 5.1)
Abdominal symptoms improved and enzymes reduced	3.9 (1.4 to 6.4)	8.2 (4.4 to 12.0)	2.0 (0.6 to 3.4)	4.2 (2.4 to 6.1)
A large reduction in time spent (-50%) on inhaled medicines	4.8 (2.3 to 7.3)	3.5 (0.7 to 6.2)	2.5 (1.1 to 3.8)	1.8 (0.4 to 3.2)
Abdominal symptoms improved	2.2 (1.2 to 5.6)	7.8 (3.4 to 12.1)	1.1 (0.7 to 2.9)	4.0 (1.7 to 6.3)
Good improvement (+10%) in QoL	2.6 (0.3 to 5.5)	4.6 (0.5 to 8.8)	1.3 (0.1 to 2.8)	2.4 (0.4 to 4.4)
Time spent on physio is halved	2.2 (0.4 to 4.0)	3.2 (0.2 to 6.2)	1.1 (0.2 to 2.0)	1.6 (0.3 to 3.0)
IV days halved	2.1 (0.2 to 4.4)	2.9 (0.5 to 5.3)	1.1 (0.2 to 2.3)	1.5 (0.1 to 2.9)
Per year increase in life expectancy	1.9 (1.4 to 2.5)	1.9 (1.3 to 2.6)	-	-
A modest reduction in time spent (-25%) on inhaled medicines	1.2 (1.3 to 3.8)	2.7 (0.1 to 5.5)	0.6 (-0.7 to 2.0)	1.4 (0.1 to 2.9)
Per 1% increase in predicted FEV1	-	-	0.5 (0.4 to 0.7)	0.5 (0.4 to 0.7)

[a]Additional life expectancy should be interpreted as the additional life expectancy conferred by the hypothetical treatments presented in the DCE, beyond existing life expectancy

e-Table 5

Comparison of characteristics of participants prescribed and not prescribed a CFTR modulator

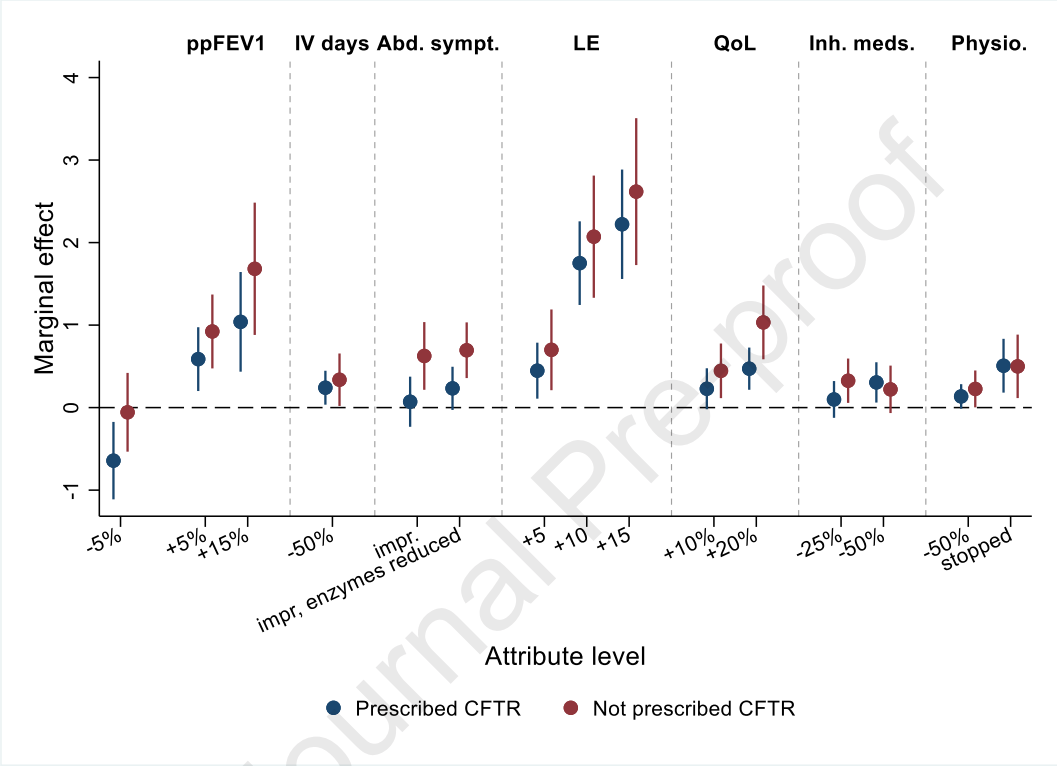
	Prescribed CFTR N=66	Not prescribed CFTR N=35
Demographics		
Age (years)	36	36
Gender (% female)	45	63
Clinical measures		
ppFEV1	68	72
absFEV1 (l)	2.5	2.4
ppFVC	84	88
absFVC (l)	3.7	3.5
Diagnosis of GERD (%)	41	43
Diagnosis of CFRD (%)	30	26
BMI	23	23
Treatment characteristics		
Treatment complexity score	24	19**
Total treatment time (mins/day)	104	71**
Physiotherapy time (mins/day)	41	29*
Inhaled medicines time (mins/day)	47	37
No. chronic treatments	14	11**
Received IV antibiotics in last year (%)	67	60
Number of IV antibiotic courses in last year	3	2
HRQoL and treatment burden measures		
EQ-5D Index score	0.76	0.79
EQ-5D VAS score	75	75
CFQ-R treatment burden domain score	51	57
CFQoL treatment burden domain score	62	68
MTBQ index score (reversed)	82	80

* P <0.1 ** P <0.05

e-Figure 1

MNL Model 1 results stratified by those prescribed or not prescribed CFTR modulators

Values are mean marginal effect, ± 95% CI. The marginal effect for no change (reference level) is represented by the dashed horizontal line. Abd. sympt, abdominal symptoms; LE, life expectancy (years); QoL, overall quality of life; Inh. meds, inhaled medications; Physio, physiotherapy; impr, symptoms improved; impr. enzymes reduced, symptoms reduced and pancreatic enzymes reduced.



e-Figure 2

MNL Model 1 results stratified by those completing before and after licensing of elexacaftor-tezacaftor-ivacaftor

Values are mean marginal effect, ± 95% CI. The marginal effect for no change (reference level) is represented by the dashed horizontal line. Abd. sympt, abdominal symptoms; LE, life expectancy (years); QoL, overall quality of life; Inh. meds, inhaled medications; Physio, physiotherapy; impr, symptoms improved; impr. enzymes reduced, symptoms reduced and pancreatic enzymes reduced.