ORIGINAL RESEARCH ARTICLE

Treating Idiopathic Pulmonary Fibrosis with the Addition of Co-Trimoxazole: An Economic Evaluation Alongside a Randomised Controlled Trial

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Abstract

Background Idiopathic pulmonary fibrosis (IPF) is a fibrotic disease of the lungs of unknown origin with a poor prognosis. A small trial of co-trimoxazole demonstrated improvements in symptoms and functional parameters over a 3-month period. We therefore conducted a larger trial with a concurrent economic evaluation to investigate this antibiotic further.

Methods We report an economic evaluation alongside a multi-centre, randomised, placebo-controlled, double-blind trial of 12 months therapy with 960 mg co-trimoxazole daily in 181 patients with fibrotic idiopathic interstitial pneumonia (IIP). Patients were recruited from 28 university and district hospitals in the UK and were aged over 40 years with fibrotic IIP. We report costs to the National Health Service (NHS) and society, change in forced vital capacity (primary endpoint) and quality-adjusted life-years (QALYs) gained, incremental cost effectiveness and cost utility ratios over 12 months.

Results From the perspective of society, mean cost per patient in the co-trimoxazole arm was approximately £1177 higher than in the placebo arm, but mean QALYs were 0.053 higher yielding an incremental cost-effectiveness ratio of £22,012 per QALY gained with a 54.44 % probability of being below £30,000. The cost of IPF to UK society in 2011 is tentatively estimated at £124 million, of which 13 % is NHS costs, 1 % social services, 2 % patient out-of-pocket costs and 84 % lost productivity.

Conclusions Given commonly employed thresholds in the UK NHS, on balance co-trimoxazole may be a cost-effective treatment for IPF, although there is substantial decision uncertainty. However, recent guidance on the use of immunosuppressive therapy in IPF patients should be taken into account prior to any policy decision.

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Key Points for Decision Makers

- Idiopathic pulmonary fibrosis (IPF) is a lung disease with dismal prognosis.
- A small randomised controlled trial showed promise that the antibiotic co-trimoxazole might have some impact on disease progression.
- The TIPAC study found no evidence for a disease-modifying effect but some survival benefit in those adhering to treatment [1].
- Because of its low cost, co-trimoxazole may be a cost-effective treatment in IPF patients.
- Recent changes in treatment guidelines, especially regarding immunosuppressive treatment should be taken into account when generalising these results to other settings.

1 Introduction

Idiopathic interstitial pneumonia (IIP) consists of a number of conditions of unknown aetiology that result in fibrosis of the lung parenchyma; the most common of which is idiopathic pulmonary fibrosis (IPF). Approximately 5,000 patients are diagnosed with IPF in the UK each year, typically aged 50–70 years, with the incidence rising over time [2]. The prognosis for patients is poor, with a 5-year survival of between 20 and 40 % [3] and no treatments shown to be effective at reducing mortality. International guidelines recognise the urgent need for new treatments [4] but most studies to date have failed to provide convincing evidence of effectiveness [5]. Furthermore, there are no data on the costs or cost effectiveness of interventions in IPF.

A small, pilot, randomised controlled trial of the antibiotic co-trimoxazole in 20 patients with IIP demonstrated improvements in forced vital capacity (FVC) and shuttle walk distance over 3 months [6]. We therefore conducted a larger clinical trial to compare the efficacy, safety and cost effectiveness of the addition of 12 months of oral co-trimoxazole to standard treatment for IPF [1]. Here, we report the results of an economic evaluation conducted alongside the clinical trial, estimating the incremental cost per point improvement in FVC and per quality-adjusted life-year (QALY) gained from co-trimoxazole versus placebo from the perspectives of the UK National Health Service (NHS) and society over a time horizon of 12 months. We also calculate a tentative estimate of the cost of IPF to UK society based on placebo group resource use data.

2 Method

Reporting of this economic evaluation is compliant with the CHEERS statement [7]. Full details of the trial are reported elsewhere [1]. Briefly, this was a double-blind, multi- (28) centre, randomised, parallel, placebo-controlled trial of 12 months therapy with co-trimoxazole in 181 patients aged over 40 years with fibrotic IIP. The study was set in the community in the UK. Patients were excluded if a secondary cause for pulmonary fibrosis was identified, if they were receiving immunosuppressant medication other than prednisolone, azathioprine or mycophenolate mofetil, had co-trimoxazole allergy or intolerance, untreated folate or B_{12} deficiency, a respiratory tract infection within 2 months prior to randomisation or if they had a significant concomitant disease that could affect subject safety or influence the study outcome. The study was conducted in accordance with Good Clinical Practice and all participants gave written informed consent. Full ethical approval was granted for the study.

Patients were randomised to receive either co-trimoxazole (Essential Generics, Egham, Surrey, UK) 960 mg (as two tablets of 480 mg each) twice daily or an identical placebo (manufactured from the pharmacy at Guy's and St Thomas's Hospital, London, UK) two tablets twice daily in addition to their usual care. Each patient received folic acid (non-proprietary) 5 mg once daily. The use of additional antibiotics was permitted for intercurrent infections. Randomisation was performed centrally using a computer-generated code with stratification for the site and the use of azathioprine/mycophenolate mofetil.

The primary outcome of the study was change in FVC at 12 months. In addition, change in overall health-related quality of life (via the EuroQol EQ-5D-3L) [8] and resource use were assessed at baseline, 6 weeks and 6, 9, and 12 months following randomisation. For the duration of the study an assessment of secondary endpoints including all-cause mortality, hospitalisations, the requirement for escalation of therapy and adverse events was made. The clinical trial did not detect a statistically significant difference in change in FVC at 12 months (mean difference +15.5 mL, 95 % confidence interval [CI] −93.6 to 124.6). Other outcome measures and details of safety monitoring are reported elsewhere [1].

Responses to the EQ-5D-3L at each time point were converted to utilities using standard UK health state valuations [9], and thence to QALYs gained by calculating the area under the curve over the 12-month time horizon.

Resource use data were collected by means of a self-administered questionnaire. Data collected at baseline pertained to the 3 months prior to randomisation, which were then used as a predictor of future cost in an adjusted analysis. Resource data were divided into four categories: NHS, social services, patient out-of-pocket expenditure and lost productivity. Within each category a number of sub-categories were defined (Table 1) with individual resource items assigned to a sub-category. Cost per patient was calculated by multiplying unit costs identified from

Table 1 Resource use categories and sub-categories

National Health Service costs	Social services costs	Out-of-pocket expenditure	Lost productivity
Prescribed medications (including study medication)	Social care	Travel	Patient time off work
Primary care		Other	Carer time off work
Secondary care			Informal caring time
Other health professional			

standard reference sources (Table 2) by resource quantities (Table 3). The price year of the analysis is 2011/2012. Discounting of costs (and outcomes) was not appropriate as the time horizon of the study was only 12 months.

Results are reported as details of resource use, mean cost and outcome (change in FVC and QALYs) per patient, increments and point estimate incremental cost-effectiveness ratio (ICER) from the perspectives of the NHS and society. 95 % CIs are calculated around increments by means of a non-parametric bootstrap of 5,000 iterations using the percentile method, the results of which are used to show uncertainty in cost effectiveness as cost-effectiveness acceptability curves. Analyses are based on an intention-to-treat (ITT) and per-protocol (PP) basis. The PP analysis excludes non-adherent patients and those withdrawing prior to death. Complete case analysis results are reported as well as increments adjusted for baseline utility and cost, with missing values imputed using multiple imputation (see "Appendix" for full details) [10]. Finally, the placebo arm of the study was used to estimate the cost of IPF to the NHS and UK society in 2011 (see below). Analysis was performed in a blinded fashion.

2.1 Cost-of-Illness Study

During data collection, patients were asked to attribute contacts with the health service due to either their IPF or other causes. This presented an opportunity to estimate the cost of IPF to society based on the cost of resource use reported by patients as attributable to IPF in the placebo arm of the study.

Patients were not asked to attribute over-the-counter (OTC) medications, prescribed drugs or informal care received for IPF. Therefore, OTC and prescribed drugs were attributed based on discussion between two authors (EW and AW). As these were all IPF patients, all informal care received was assumed attributable to IPF.

Data on primary, secondary and tertiary resource use were available on 72 patients. OTC and prescription data were available on all 85 patients in the placebo arm. Data on travel costs and lost productivity were available on 69 and 67 patients, respectively. Summary totals in the analysis are based on observations for which complete data are available, thus the reported sum may not equal the sum of the individual components (e.g. in the case of cost of out-of-pocket, indirect, overall NHS and societal costs).

Per patient costs were multiplied by the prevalence of IPF in the UK in 2011 to provide an estimate of the cost to the NHS and society of IPF. We were not able to identify any UK-specific data on the prevalence of IPF. However, a recent study estimated the overall incidence at 7.44 per 100,000 person-years [2]. A study on both the incidence and prevalence of IPF in the USA used both a broad and narrow definition of IPF [11]. The narrow definition generated an overall incidence of 6.8 per 100,000 person-years with an associated prevalence of 14.0 per 100,000 person-years. Given the similarity in the estimates of the incidence between the US and UK studies, it was assumed that the 'narrow definition' of IPF was the most consistent with that used in the UK and thus prevalence would also be similar (this is contingent on an assumption of similar prognosis for IPF patients in both the US and UK). Thus, a prevalence of 14.0 per 100,000 was applied to the 2011 UK population of 63.2 million [12] to estimate the prevalence in 2011 of 8,800.

3 Results

Patients were generally well matched at baseline although patients in the co-trimoxazole group may have had shorter disease duration prior to study entry [1]. Complete data were available for 79 patients (active, placebo: 41, 38) for the PP cost-utility analysis from the societal perspective and for 125 patients (61, 64) for the ITT cost-utility analysis from the NHS perspective. These numbers vary because of the pattern of missing data, for example, a patient with full resource use and FVC data would be included in the cost-effectiveness complete case analysis, but if utility data were missing (even just for one time point) the patient was excluded from the cost utility analysis. Imputed analyses comprised 180 patients (95, 85) [one patient was not imputable because of missing covariates].

3.1 Resource Use and Cost

Point estimate analyses of resource use (Table 3) show very little difference in primary, secondary or other healthcare resource use between the groups. From the perspective of the NHS, co-trimoxazole is associated with an additional cost of £100 per patient per year (SE £495).

Table 2 Unit costs and sources

Cost item	Unit cost	Source
Cost of OP appt for IPF	£133.00	Ref costs 2011–2012 [31], respiratory medicine consultant led FU attendance, non-admitted face to face. File NSRC01 2011–2012, worksheet CLFUSFF code 340
Cost of OP appt for other	£139.00	PSSRU 2012 [32], P109, weighted average of all adult OP attendances (follow-up face-to-face attendance)
Cost of day case appt for IPF	£506.00	Ref costs 2011–2012 [31], day case HRG data. HRG DZ19B: other respiratory diagnoses with intermediate CC. File NSRC01 2011–2012, worksheet DC code DZ19B
Cost of day case appt for other	£680.00	PSSRU 2012 [32], P109, weighted average of all stays
Cost of IP admission for IPF	£1,814.00	Ref costs 2011–2012 [31], elective IP data. HRG DZ19B: other respiratory diagnoses with intermediate CC. File NSRC01 2011–2012, worksheet EI code DZ19B
Cost of IP admission for other	£3,191.00	PSSRU 2012 [32], P109, elective IP stays
Cost per day, IP admission	£352.00	Ref costs 2011–2012 [31], elective IP excess bed day data. HRG DZ19B: other respiratory diagnoses with intermediate CC. File NSRC01 2011–2012, worksheet EI XS code DZ19B
Cost of A&E attendance	£112.00	PSSRU 2012 [32], P109, A&E services leading to not admitted
Hourly wage	£12.76	ONS, Annual Survey of Hours and Earnings (ASHE) 2012 [33], P6, median gross hourly earnings
Cost of GP surgery consultation	£43.00	PSSRU 2012 [32], P183, per surgery consultation 11.7 min with qualification costs and direct care staff costs
Cost of GP home visit	£110.00	PSSRU 2012 [32], P183, per out of surgery visit 23.4 min including qualification and direct care staff costs
Cost of GP phone consultation	£26.00	PSSRU 2012 [32], P183, per teleconference 7.1 min including qualification and direct care staff costs
Cost of nurse surgery consultation	£13.69	PSSRU 2012 [32], P180, per 15.5 m face-to-face contact including qualifications
Cost of nurse home visit	£35.02	Assumed same inflation factor as for GP surgery: home visit
Cost of nurse phone consultation	£13.69	Assumed same as surgery consultation
Cost of health visitor surgery consultation	£44.00	PSSRU 2012 [32], P177, based on NHS reference costs
Cost of health visitor home visit	£44.00	Assumed same as surgery consultation
Cost of health visitor phone consultation	£44.00	Assumed same as surgery consultation
Cost of physio surgery consultation	£47.00	PSSRU 2012 [32], P167, based on NHS reference costs
Cost of physio home visit	£47.00	Assumed same as surgery consultation
Cost of physio phone consultation	£47.00	Assumed same as surgery consultation
Cost of OT surgery consultation	£69.00	PSSRU 2012 [32], P168, based on NHS reference costs
Cost of OT home visit	£69.00	Assumed same as surgery consultation
Cost of OT phone consultation	£69.00	Assumed same as surgery consultation
Cost of other AHP surgery consultation	£47.00	Assumed same as physiotherapist
Cost of other AHP home visit	£47.00	Assumed same as physiotherapist
Cost of other AHP phone consultation	£47.00	Assumed same as physiotherapist
Cost of carer home visit	£23.00	PSSRU 2012 [32], P193, per hour of face-to- face weekday contact
Cost of social worker office visit	£54.00	PSSRU 2012 [32], P190, per hour of client related work
Cost of social worker home visit	£138.14	Assumed same proportionate increase as GP home/surgery visit

Table 2 continued

Cost item	Unit cost	Source
Cost of social worker phone call	£54.00	Assumed same as office visit
Cost of cleaner home visit	£23.00	Assumed same as carer home visit
Cost of car transport to hospital	£2.40	Assumed 6 miles × 40 p per mile
Cost of car transport to GP surgery	£1.20	Assumes half distance to hospital
Cost of child care per hour	£5.00	Child or other dependent care cost per hour during hospital or GP visit
Co-trimoxazole per day	£0.6208	BNF 62 [34], 100 × 480 mg = £15.52 at 4 × 480 mg/day = £0.6208/day

A&E accident and emergency, *AHP* allied health professional, *appt* appointment, *BNF* British National Formulary, *CC* complications, *FU* follow-up attendance, *GP* general practitioner, *HRG* health resource group, *IP* inpatient, *IPF* idiopathic pulmonary fibrosis, *NHS* National Health Service, *ONS* office of national statistics, *OP* outpatient, *OT* occupational therapist, *physio* physiotherapist, *PSSRU* Personal Social Services Research Unit, *Ref costs* National Schedule of Reference Costs

Table 3 Resource use quantities

Variable	N (intervention, control)	Intervention mean (SD)	Control mean (SD)	Increment
Primary care				
GP surgery visits due to IPF	(64, 72)	1.13 (1.65)	1.44 (2.23)	
Due to other	(64, 72)	2.16 (2.58)	2.44 (3.24)	
Total	(64, 72)	3.28 (3.08)	3.89 (3.83)	−0.608
GP home visits due to IPF	(64, 72)	0.13 (0.55)	0.18 (0.66)	
Due to other	(64, 72)	0.23 (1.09)	0.1 (0.38)	
Total	(64, 72)	0.36 (1.2)	0.28 (0.83)	0.082
GP phone calls due to IPF	(64, 72)	0.19 (0.56)	0.24 (0.66)	
Due to other	(64, 72)	0.13 (0.63)	0.1 (0.34)	
Total	(64, 72)	0.31 (0.89)	0.33 (0.87)	−0.021
Nurse surgery visits due to IPF	(64, 72)	0.14 (0.5)	0.24 (0.66)	
Due to other	(64, 72)	3.36 (4.77)	2.99 (3.71)	
Total	(64, 72)	3.5 (4.71)	3.22 (3.7)	0.278
Nurse home visits due to IPF	(64, 72)	0.83 (3.78)	0.08 (0.6)	
Due to other	(64, 72)	0.86 (4.78)	0.43 (2.19)	
Total	(64, 72)	1.69 (5.98)	0.51 (2.62)	1.174
Nurse phone calls due to IPF	(64, 72)	0.02 (0.13)	0.04 (0.26)	
Due to other	(64, 72)	0.03 (0.25)	0.13 (0.95)	
Total	(64, 72)	0.05 (0.28)	0.17 (1.09)	−0.12
Secondary care				
OP appts due to IPF	(64, 72)	2 (4.49)	1 (1.36)	
Due to other	(64, 72)	0.89 (1.45)	0.99 (1.63)	
Total	(64, 72)	2.89 (4.91)	1.99 (2.13)	0.905
Day case appts due to IPF	(64, 72)	0.09 (0.34)	0.03 (0.17)	
Due to other	(64, 72)	0.11 (0.44)	0.17 (0.41)	
Total	(64, 72)	0.2 (0.54)	0.19 (0.46)	0.009
IP admissions due to IPF	(64, 72)	0.19 (0.75)	0.19 (0.46)	
Due to other	(64, 72)	0.08 (0.32)	0.1 (0.3)	
Total	(64, 72)	0.27 (0.84)	0.29 (0.59)	−0.026

Table 3 continued

Variable	N (intervention, control)	Intervention mean (SD)	Control mean (SD)	Increment
A&E attendances due to PF	(64, 72)	0.13 (0.58)	0.14 (0.42)	
Due to other	(64, 72)	0.02 (0.13)	0.03 (0.17)	
Total	(64, 72)	0.14 (0.61)	0.17 (0.47)	−0.026
Other health professional				
Health visitor office visits due to IPF	(64, 72)	0.05 (0.28)	0.01 (0.12)	
Due to other	(64, 72)	0.03 (0.18)	0 (0)	
Total	(64, 72)	0.08 (0.37)	0.01 (0.12)	0.064
Health visitor home visits due to IPF	(64, 72)	0.25 (1.39)	0.06 (0.23)	
Due to other	(64, 72)	0.02 (0.13)	0 (0)	
Total	(64, 72)	0.27 (1.39)	0.06 (0.23)	0.21
Health visitor phone calls due to IPF	(64, 72)	0.03 (0.25)	0.03 (0.24)	
Due to other	(64, 72)	0 (0)	0 (0)	
Total	(64, 72)	0.03 (0.25)	0.03 (0.24)	0.003
Physiotherapist office visits due to IPF	(64, 72)	0.06 (0.3)	0.13 (0.5)	
Due to other	(64, 72)	0.02 (0.13)	0.18 (1.42)	
Total	(64, 72)	0.08 (0.32)	0.31 (1.49)	−0.227
Physiotherapist home visits due to IPF	(64, 72)	0.06 (0.39)	0.06 (0.37)	
Due to other	(64, 72)	0 (0)	0.04 (0.35)	
Total	(64, 72)	0.06 (0.39)	0.1 (0.51)	−0.035
Physiotherapist phone calls due to IPF	(64, 72)	0.02 (0.13)	0 (0)	
Due to other	(64, 72)	0 (0)	0 (0)	
Total	(64, 72)	0.02 (0.13)	0 (0)	0.016
OT office visits due to IPF	(64, 72)	0.16 (1.01)	0 (0)	
Due to other	(64, 72)	0 (0)	0.03 (0.17)	
Total	(64, 72)	0.16 (1.01)	0.03 (0.17)	0.128
OT home visits due to IPF	(64, 72)	0.03 (0.18)	0.06 (0.37)	
Due to other	(64, 72)	0.16 (0.91)	0.28 (1.4)	
Total	(64, 72)	0.19 (0.92)	0.33 (1.43)	−0.146
OT phone calls due to IPF	(64, 72)	0 (0)	0 (0)	
Due to other	(64, 72)	0.02 (0.13)	0.01 (0.12)	
Total	(64, 72)	0.02 (0.13)	0.01 (0.12)	0.002
Other health professional office visits due to IPF	(64, 72)	0.25 (0.87)	0.18 (0.81)	
Due to other	(64, 72)	0.2 (0.82)	0.19 (0.68)	
Total	(64, 72)	0.45 (1.19)	0.38 (1.23)	0.078
Other health professional home visits due to IPF	(64, 72)	0.25 (0.99)	0.14 (0.45)	
Due to other	(64, 72)	0.02 (0.13)	0.01 (0.12)	
Total	(64, 72)	0.27 (1)	0.15 (0.46)	0.113
Other health professional phone calls due to IPF	(64, 72)	0.11 (0.51)	0 (0)	
Due to other	(64, 72)	0 (0)	0.06 (0.47)	
Total	(64, 72)	0.11 (0.51)	0.06 (0.47)	0.054
Pulmonary rehabilitation sessions	(64, 72)	0.92 (3.14)	0.47 (1.8)	0.45
Social services				
Social services office visit due to IPF	(64, 72)	0 (0)	0.03 (0.17)	
Due to other	(64, 72)	0 (0)	0 (0)	
Total	(64, 72)	0 (0)	0.03 (0.17)	−0.028
Social services home visit due to IPF	(64, 72)	0.34 (2.51)	0 (0)	
Due to other	(64, 72)	0 (0)	0 (0)	
Total	(64, 72)	0.34 (2.51)	0 (0)	0.344

Table 3 continued

Variable	N (intervention, control)	Intervention mean (SD)	Control mean (SD)	Increment
Social services phone call due to IPF	(64, 72)	0 (0)	0.03 (0.24)	
Due to other	(64, 72)	0 (0)	0.01 (0.12)	
Total	(64, 72)	0 (0)	0.04 (0.26)	−0.042
Carer home visit due to IPF	(64, 72)	1.22 (7.23)	0 (0)	
Due to other	(64, 72)	0.52 (4)	0 (0)	
Total	(64, 72)	1.73 (9.56)	0 (0)	1.734
Cleaner home visit due to IPF	(64, 72)	0 (0)	0 (0)	
Due to other	(64, 72)	0.03 (0.25)	0.01 (0.12)	
Total	(64, 72)	0.03 (0.25)	0.01 (0.12)	0.017

A&E accident and emergency, *appt* appointment, *GP* general practitioner, *IP* inpatient, *IPF* idiopathic pulmonary fibrosis, *OP* outpatient, *OT* occupational therapist, *SD* standard deviation

Table 4 Summary costs by sector, mean (SE)

	N (intervention, control)	Intervention	Control	Increment
Study drug	(64, 72)	186.82 (8.61)	0 (0)	186.82 (8.12)
Prescription medicines (excluding study drug)	(63, 71)	1,421.24 (210.88)	1,584.15 (227.36)	−162.91 (312.61)
Primary care	(64, 72)	296.40 (41.89)	270.83 (26.47)	25.57 (48.45)
Secondary care	(64, 72)	1,129.03 (266.95)	1,113.65 (171.04)	15.38 (310.20)
Other health professionals	(64, 72)	130.89 (29.83)	98.69 (22.63)	32.20 (36.97)
Social services	(64, 72)	297.10 (128.85)	86.83 (48.97)	210.26 (132.07)
Patient OoP costs	(57, 68)	274.86 (109.49)	226.22 (86.32)	48.64 (137.60)
Indirect costs	(54, 62)	14,496.97 (3,000.84)	12,114.55 (2,645.76)	2,382.42 (3,984.86)
NHS	(63, 71)	3,187.49 (385.76)	3,087.23 (316.28)	100.27 (494.73)
Societal (drugs + NHS + social services + patient OoP + indirect)	(51, 57)	16,240.31 (2,817.86)	16,724.58 (3,073.18)	−484.27 (4,202.69)

NHS National Health Service, *OoP* out of pocket

However, from a societal perspective, co-trimoxazole is associated with a saving of £484 per patient per year (SE £4,203; Table 4).

3.2 Outcomes

Co-trimoxazole was observed with increases in mean QALYs gained compared with placebo, but as with resource use, there is a great deal of uncertainty and 95 % CIss did not exclude zero.

3.3 Cost Effectiveness

In all analyses, 95 % CIs did not exclude zero. Point estimate results, adjusted for baseline and with missing data imputed, showed a higher cost and very little difference in incremental FVC for the treatment group compared with placebo (Table 5). Overall health gain

was on average higher in the treatment group (Table 6). The ICER varied between co-trimoxazole being dominant to £22,012 per QALY gained, depending on perspective and ITT/PP population (Table 6). There is between 54.4 and 91.9 % probability that the ICER is below £30,000, depending on perspective and analysis (Fig. 1).

3.4 Cost of Illness

Based on analysis of the placebo arm enrolled in the trial, the cost to UK society of IPF in 2011 is estimated at £124 million (SE £25.3 million), of which approximately £14 million (12 %) is attributable to the NHS, £0.6 million (1 %) to social services, £1.6 million (2 %) to out-of-pocket costs to patients and the remainder (85 %) attributable to morbidity associated with lost productivity (Table 7).

Table 5 Cost-effectiveness

Analysis	N		dFVC		Cost		Unadjusted			Imputed, adjusted for baseline FVC		
	Co-trim	Placebo	Co-trim	Placebo	Co-trim	Placebo	Inc £ (95 % CI)	Inc dFVC (95 % CI)	ICER	Inc £ (95 % CI)	Inc dFVC (95 % CI)	ICER
ITT NHS	51	55	−0.170	−0.199	£3,608	£3,290	£318 (−£772, £1453)	0.029 (−0.098, 0.150)	£11,007	£407 (−£523, £1272)	0.047 (−0.116, 0.115)	£8,654
ITT societal	41	45	−0.207	−0.199	£18,498	£17,996	£502 (−£9195, £10304)	−0.008 (−0.150, 0.122)	[Placebo dominant]	£2,846 (−£5104, £7418)	0.047 (−0.120, 0.124)	£60,527
PP NHS	48	49	−0.175	−0.174	£3,637	£3,409	£228 (−£971, £1490)	−0.001 (−0.125, 0.122)	[Placebo dominant]	£287 (−£643, £1206)	−0.008 (−0.123, 0.115)	[Placebo dominant]
PP societal	39	41	−0.212	−0.170	£18,858	£19,322	−£464 (−£11095, £9765)	−0.042 (−0.181, 0.095)	£11,106 [favour placebo]	£674 (−£5844, £6628)	−0.008 (−0.123, 0.118)	[Placebo dominant]

CI confidence interval, *Co-trim* co-trimoxazole, *ITT* intention-to-treat, *PP* per-protocol, *NHS* National Health Service cost perspective, *societal* societal cost perspective, *dFVC* change in FVC, *Inc* incremental, *ICER* incremental cost-effectiveness ratio

Table 6 Cost utility

Analysis	N		Cost		QALYs		Unadjusted				Imputed, adjusted for baseline utility and cost			
	Co-trim	Placebo	Co-trim	Placebo	Co-trim	Placebo	Inc £ (95 % CI)	Inc QALYS (95 % CI)	ICER	P(CE|£30k) (%)	Inc £ (95 % CI)	Inc QALYS (95 % CI)	ICER	P(CE|£30k) (%)
ITT NHS	61	64	£3,186	£3,136	0.571	0.539	£50 (−£927, £1079)	0.032 (−0.061, 0.126)	£1,567	70.78	£365 (−£510, £1273)	0.053 (−0.010, 0.115)	£6,818	86.98
ITT societal	51	53	£16,240	£17,210	0.590	0.539	−£970 (−£9121, £7438)	0.051 (−0.056, 0.157)	[Active dominant]	68.02	£1177 (−£4910, £7273)	0.053 (−0.009, 0.116)	£22,012	54.44
PP NHS	58	61	£3,205	£3,161	0.571	0.527	£44 (−£1001, £1103)	0.045 (−0.051, 0.142)	£993	79.46	£287 (−£612, £1183)	0.059 (−0.002, 0.118)	£4,849	91.86
PP societal	49	48	£16,434	£18,587	0.584	0.527	−£2152 (−£11313, £6679)	0.057 (−0.055, 0.163)	[Active dominant]	76.74	£674 (−£5605, £6689)	0.059 (−0.002, 0.119)	£11,400	71.04

CI confidence interval, *Co-trim* co-trimoxazole, *ITT* intention-to-treat, *PP* per-protocol, *NHS* National Health Service cost perspective, *societal* societal cost perspective, *Inc* incremental, *ICER* incremental cost-effectiveness ratio, *P(CE|£30k)* probability that the ICER is below £30,000 per QALY gained, *QALY* quality-adjusted life-year

4 Discussion

4.1 Interpretation of Results

The results present a number of separate analyses. When analysing cost alone, mean cost to the NHS per patient in the co-trimoxazole arm is approximately £100 higher than in the placebo arm. When overall societal costs are included, mean cost per patient in the co-trimoxazole arm is approximately £400 less than in the placebo arm (Table 4). However, when cost data are combined with outcomes, point estimate incremental costs vary somewhat between analyses (Tables 5, 6). This is simply because of the exclusion of data in the complete case analyses and high uncertainty in incremental cost (and outcomes): the high standard errors mean that, for example, none of the 95 % CIs around the increments exclude zero.

One conclusion would be that as we have failed to demonstrate a statistically significant effect on cost, outcomes or cost effectiveness, we can make no policy recommendation from these data. However, as the study was powered on the primary outcome (change in FVC at 12 months) and not cost, QALYs or cost effectiveness, such a conclusion may be a type one error. Alternatively, a decision theoretic approach would argue that a decision has to be made whether to adopt co-trimoxazole as part of routine therapy in these patients or not, and that the decision has to be made on the evidence available irrespective of the uncertainty: a decision to delay pending further information is still a decision to withhold a treatment for the current cohort of patients. This implies that decisions should be based on mean values alone (and uncertainty used to determine the value of gathering further information) [13, 14]. The latter (decision theoretic) approach risks being "fooled by randomness", whilst the former (inferential approach) is inconsistent with the principles of decision theory, and will not lead to maximising expected outcomes subject to the resources available.

Following decision theoretic reasoning, the point estimate of the ICER should be used to determine whether co-trimoxazole represents good value for money. However, in Tables 5 and 6 we present numerous ICERs from separate analyses representing different analytic perspectives (NHS and society), different outcomes (change in FVC and QALYs gained) and statistical techniques to handle missing data. It is argued that the most appropriate analytic perspective for an economic evaluation is that of society as any lesser perspective may lead to misleading conclusions owing to simple cost shifting between budgets rather than genuine changes in resource consumption [15]. Similarly, the QALY may be seen as a preferable outcome measure to a change in FVC as the QALY is a measure of overall quality-adjusted life expectancy, rather than focusing on one particular symptom or functional aspect. Finally, the ITT analytic approach is the least subject to bias [16], the imputed analysis avoids discarding informative data [10] and adjustment for baseline values takes into account any differences in patient characteristics at baseline [17].
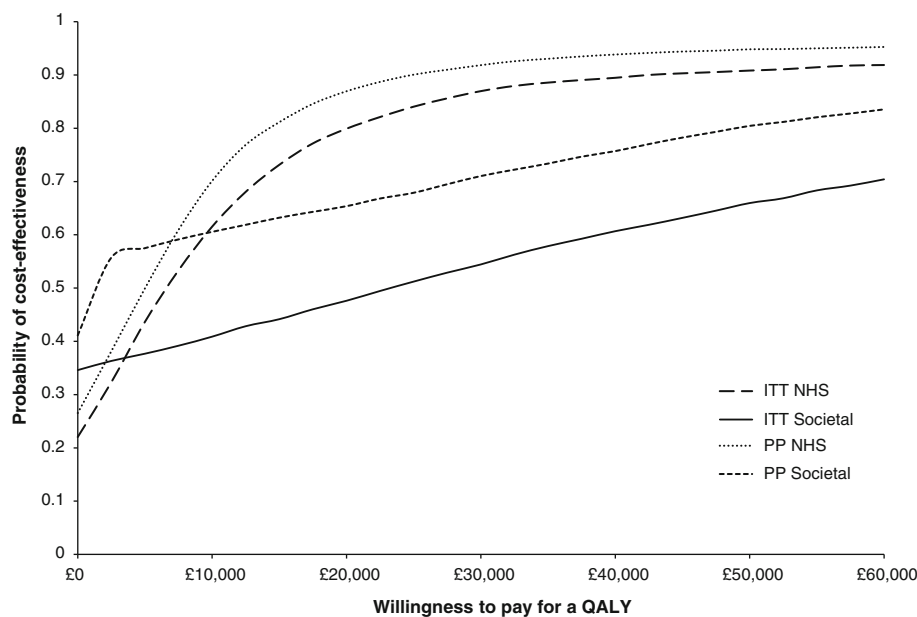
On this basis, the most appropriate analysis is the adjusted, imputed ITT cost-utility analysis conducted from the societal perspective (Table 6, row 2). Point estimates suggest co-trimoxazole increases the mean cost per patient by £1177, for a gain of 0.053 QALYs in these patients. The incremental cost per incremental QALY gained is therefore £22,012. This is below the upper limit considered 'acceptable' by the National Institute for Health and Care Excellence (NICE) [NICE argues that a threshold of £20,000–£30,000 per QALY is an appropriate willingness to pay] [18], and therefore co-trimoxazole may be considered a cost-effective treatment. Analysis of uncertainty suggests a 54.44 % probability that the ICER is below £30,000.

4.2 Clinical Implications

Despite the cost-effectiveness results, analysis of the study primary and some secondary clinical endpoints suggests that co-trimoxazole has no effects on the traditional surrogate measures of disease progression [1]. This brings into question the usefulness of these markers. Although the majority of patients die of sub-acute respiratory failure, up to 30 % die of an acute exacerbation of their disease [19]. These exacerbations cannot be predicted based upon the severity of lung function impairment [20]. The annual incidence of exacerbations, per patient, is between 5 and 19 % [21] and they have an associated 3-month mortality of up to 80 % [20]. Indeed, hospitalisation along with age and lung function, are independent predictors of survival in IPF [22].

Our results suggest that either infection has an important role in IPF pathogenesis or co-trimoxazole has clinically relevant non-antimicrobial effects. Recent data published following the completion of the study have led to a change in the medical management of IPF, with a reduction in the use of immunosuppressive therapy [23]. The drug history of patients at randomisation reflected UK prescribing practices at the time [24], with half of the patients receiving prednisolone. However, as mentioned, UK guidelines no longer recommend the routine use of immunosuppressive therapy. Therefore, the typical patient seen in practice may differ from those enrolled in the study; specifically, patients are less likely to be immunosuppressed. If the capacity to benefit in non-immunosuppressed patients is lower (they are less at risk of opportunistic infections), the ICER is likely to be higher (i.e. co-trimoxazole may be less cost effective than our results suggest). Whether it crosses the £20,000–£30,000 threshold is an empirical question for which further research is required.

Fig. 1 Cost-effectiveness
acceptability curves. The cost-
effectiveness acceptability
curve is the probability that the
incremental cost-effectiveness
ratio (ICER) is below a given
willingness to pay for a quality-
adjusted life-year (i.e. the
probability that co-trimoxazole
is cost effective given a
threshold of X). There is
between 54.44 and 91.86 %
probability that the ICER is
below £30,000, depending on
analytic perspective. *ITT*
intention-to-treat analysis, *NHS*
National Health Service, *PP*
per-protocol analysis, *QALY*
quality-adjusted life-year

Table 7 Cost-of-illness
estimate

Societal totals do not equal the
sum of the four components
because of missing data

m million, *OoP* out of pocket

Sector	Sample size	Mean (SE) per patient	Total cost to UK society 2009 (SE)
NHS	72	£1637 (£207)	£14.4 m (£1.8 m)
Social services	72	£73 (£47)	£0.7 m (£0.4 m)
Patient OoP	68	£183 (£85)	£1.6 m (£0.7 m)
Indirect	62	£11,378 (£2,622)	£100.1 m (£23.1 m)
Society	58	£14,046 (£2,880)	£123.6 m (£25.3 m)

4.3 Comparison with Other Studies

There are very few data on the costs of interstitial lung
disease or the cost effectiveness of treatments. Although
researchers have investigated the economics of diagnostic
assessments for IPF [25, 26], the only data relating to IPF
treatment are in abstract form and show rising healthcare
costs using a database of medical and pharmacy claims
from private health plans in USA; the researchers found
that 70 % of mean annual total healthcare costs were due to
hospitalisation and that costs increased with age and were
significantly higher in those who died at the end of the
annual follow-up [27]. At the time of writing, we are not
aware of any published estimates of the costs of the illness
to society or cost effectiveness of other IPF treatments with
which to compare our results.

The cost of IPF to society in 2011 was estimated at £124
million. By way of comparison, a longitudinal cost-of-ill-
ness study of the cost of *occupational* asthma estimated a
lifetime societal cost (rather than a cross-sectional annual
cost) for the 2003 cohort of new cases at £95–£135 m
(£2004) [28]. Total expenditure on bronchodilators, respi-
ratory corticosteroids and leukotriene receptor antagonists
in England in 2011 was £971 million [29], and UK gross

domestic product was £1.516 trillion [30]. IPF therefore
likely represents a small component of total expenditure on
lung disease. Possible explanations for this include the
relative rarity of the disease, the poor prognosis and lack of
effective interventions.

4.4 Strengths and Weaknesses

To our knowledge, this is the first cost-effectiveness ana-
lysis of a potential treatment for IPF. It is also the first
study to estimate the cost of IPF to UK society and the
NHS. It is non-commercially funded and based on a well-
conducted, double-blind, randomised controlled trial using
prospective data collection over 12 months via detailed
questionnaires and should therefore be of high internal
validity.

A 12-month time horizon was chosen for several rea-
sons. First, the horizon was constrained by budgetary
requirements. Second, the disease is associated with a poor
prognosis and therefore 12 months may allow any changes
in mortality between groups to be apparent. Third, the
study was powered on the primary outcome (change in
FVC at 12 months), and such a time horizon was consid-
ered to be a clinically relevant endpoint.

The major weakness of the study is the relatively low proportion of the data included in the complete case analysis. However, this is due to the strict definition of a 'complete case', requiring complete data on primary, secondary and other NHS care, drug costs, out-of-pocket costs and lost productivity as well as FVC and EQ5D measures at every follow-up. If any one of these items were missing then the observation was excluded from the complete case analysis, leading to exclusion of the data that were present. However, the imputed analysis (using the multiple imputation technique [10]) includes these data, repeatedly replacing the missing data with plausible values sampled from the distribution around the conditional mean. This therefore makes best use of the data available whilst allowing for uncertainty in the missing values.

We are not aware of any estimates of the cost of IPF to the UK economy. The placebo arm of this trial therefore provided an opportunity to estimate this cost. Because of this somewhat opportunistic approach, the estimates must be interpreted with appropriate caution. The danger with using placebo arms of studies to estimate the cost of illness is that cost items common to both arms of a trial are typically excluded from analysis (as they cancel each other out in the incremental analysis), and thus the cost per arm may not accurately reflect all cost items. Second, trials may involve activity and contacts with the health service that would not be seen in routine care (protocol-driven costs). Third (and possibly most importantly), inclusion and exclusion criteria may select a sample of patients enrolled in a study that is not representative of the 'typical' patient population. Additionally in this study, OTC, prescription drug costs and informal care costs were attributed to IPF based on the clinical and economics experience of two of the authors (AW and EW, respectively). Where patients have co-morbidities, we may have overestimated the indirect cost attributable to IPF. In response to these limitations, owing to the nature of the data collection in this trial, we are confident that no major cost items were excluded and that the placebo arm of this study represents a reasonable picture of routine practice for IPF patients. Comparison of the sub-group used in the cost-of-illness study with the rest of the trial population shows no substantial differences except for a longer time since diagnosis (data not shown), and we believe the trial population to be representative of the patient population at the time of randomisation (but we refer readers to comments above regarding current policy for immunosuppressive therapy).

5 Conclusion

On average, co-trimoxazole for patients with IPF for 1 year leads to increases in both mean cost and QALYs gained.

The point estimate ICER is £22,012 from the perspective of society (£6,818 from the NHS perspective). Analysis of uncertainty suggests a 54.44 % probability that the ICER is below £30,000 per QALY from the perspective of society (86.98 % from the NHS perspective). Point estimate ICERs are below the maximum willingness to pay for a QALY in the UK (considered to be around £20,000–£30,000) [18], and therefore the addition of co-trimoxazole to standard treatment may be considered a cost-effective treatment. However, changes in UK management practice, particularly with regard to immunosuppressive therapy means that current patient populations may differ from the one enrolled into this study. Assessment of the comparability of the patient population with that enrolled in the study should precede any policy decision based on this analysis.

Appendix

Details of Imputation

Missing data were imputed in STATA using the 'ice' command at the level of total NHS and societal costs, QALYs and change in FVC at 12 months. Explanatory variables were baseline NHS and societal cost, utility and FVC, whether the patient was prescribed prednisolone, age left education, marital status, employment status and intervention arm. Five datasets were generated, each based on 1000 markov chain monte carlo (MCMC) iterations. The code is provided below:

```
ice C_NHS C_Societal QALYs dfvcabs5 ///
        C_NHS1 C_Societal1 Utility1 fvcabs1 ///
        status_cat o.ageleftEd_cat o.marital_cat o.employment_cat arm_imp, ///
        boot seed(12345) m(5) cycles(1000) saving(imp_TIPAC_CUA, replace) trace
(trace_TIPAC_CUA)
```

Details of Adjustment to Baseline Values

The imputed, adjusted increments were calculated as follows:

- The imputed datasets resulting from the 'ice' command above were resampled with replacement (thus five 'new' datasets were generated).
- OLS regressions were used to estimate NHS cost, societal cost, QALYs and change in FVC for each of the 'new' datasets, using treatment group and baseline NHS or societal cost, utility or FVC as explanatory variables respectively.
- The coefficients on treatment group were recorded as the adjusted incremental cost or outcome respectively.
- Steps 1-3 were repeated 1000 times, thus generating 5000 sets of adjusted incremental cost and outcomes (1000 from each imputed dataset).
- The percentile method was used to calculate 95 % confidence intervals around point estimate increments.

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