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SYSTEMATIC REVIEW

The Burden of Illness of Idiopathic Pulmonary Fibrosis: A Comprehensive Evidence Review

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Abstract

Background Idiopathic pulmonary fibrosis (IPF) is a debilitating condition with significant morbidity and poor survival. Since 2010, there has been increased activity in the development of treatments that aim to delay progression of the disease.

Objective Our study involves a comprehensive review of the literature for evidence on health-related quality of life (HRQoL), healthcare resource use (HCRU) and costs, and an assessment of the burden of illness of the condition.

Methods We carried out a systematic literature review (SLR) to identify economic evaluations and HRQoL studies. We searched EMBASE, MEDLINE and MEDLINE In Process for relevant studies from database origins to April 2017. Alongside the presentation of the study characteristics and the available evidence, we carried out a qualitative comparison using reference population estimates for HRQoL and national health expenditure for costs.

Results Our search identified a total of 3241 records. After removing duplicates and not relevant articles, we analysed 124 publications referring to 88 studies published between 2000 and 2017. Sixty studies were HRQoL and 28 were studies on costs or HCRU. We observed an exponential growth of publications in the last 3–5 years, with the majority of the studies conducted in Europe and North America. Among the HRQoL studies, and despite regional differences, there was some agreement between estimates on the absolute and relative level of HRQoL for patients with IPF compared with the general population. Regarding costs, after adjustments for the cost years and currency, the suggested annual per capita cost of patients with IPF in North America was estimated around US$20,000, 2.5–3.5 times higher than the national healthcare expenditure. Additionally, studies that analysed patients with IPF alongside a matched control cohort suggested a significant increase in resource use and cost.

Conclusion The reviewed evidence indicates that IPF has considerable impact on HRQoL, relative to the general population levels. Furthermore, in studies of cost and resource use, most estimates of the burden were consistent in suggesting an excess cost for patients with IPF compared with a control cohort or the national health expenditure. This confirms IPF as a growing threat for public health worldwide, with considerable impact to the patients and healthcare providers.

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Key Points

Acquiring knowledge on the overall burden of idiopathic pulmonary fibrosis (IPF) is essential for stakeholders planning resource allocation across many conditions. This study provides an overview of the evidence on health-related quality of life (HRQoL) and costs in IPF.

Several studies showed that IPF has a considerable impact on patients' HRQoL, including physical and social components, in comparison with the general population.

Compared with the national health expenditure or control-matched patient cohorts, IPF was associated with an excess healthcare cost.

Our findings confirm IPF as a growing threat for public health worldwide, with considerable impact to the patients and healthcare providers.

1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown aetiology associated with significant morbidity and poor survival [1]. The symptoms include dyspnoea, dry cough, tiredness, aching of muscles and joints, unintended weight loss and finger clubbing [1]. The progression of the disease varies significantly between patients and depends on many clinical and external factors [2]. Overall, individuals with IPF have similar life expectancy to those with non-small cell lung cancer, with reported estimates of median survival being 50% at 3 years and 20% at 5 years post-diagnosis [1, 3–5]. The estimates of incidence and prevalence of IPF vary depending on the definition used, the study design, and the underlying population characteristics (such as age, gender, geographic location, etc.) [3, 6]. In general, studies agree that the condition is more common in men and in older people. In Europe, the British Thoracic Society estimates that the prevalence is around 50 per 100,000 population, with the highest rates in Northern Ireland, North West England, Scotland and Wales [7]. This is considerably higher than older estimates from other parts of Europe such as Norway (19.7–23.9/100,000) [8] and Belgium (1.25/100,000) [9]. In North America, two US studies placed the prevalence estimates between 42.7 [10] and 63 [11] patients per 100,000 population (using the broad definition); while a more recent Canadian study reported the prevalence to be as high as 115/100,000 (broad definition) [12]. Similarly, in Japan studies suggested prevalence estimates from 2.9/100,000 in 2005 [13] to 10/100,000 population in 2007 [4]. It follows that, although IPF is still treated as a rare condition in many countries, the evolution of diagnostic methods and greater physician awareness around the disease and an aging population may be leading to an increase in the prevalence and incidence rates over time [6, 14, 15].

There is also considerable activity in the development of treatments for the condition. Before 2010 there was no licensed pharmacological treatment for this devastating disease [1]. In 2008, pirfenidone was approved in Japan and in 2011 by the European Medicines Agency (EMA). In 2014 the US Food and Drug Administration (FDA) approved both pirfenidone and nintedanib, with EMA also confirming approval for nintedanib soon after [16–18].[1] Despite the recent termination of the clinical trial programmes for tralokinumab [19] and simtuzumab [20], a number of new agents are being tested in experimental trials for the treatment of IPF (SAR156597 [21], lebrikizumab [22], FG-3019 [23], PRM-151 [24] and others).

For healthcare providers, who often have to make difficult decisions about resource allocation across many conditions, in-depth knowledge of the overall burden of the disease is essential. Our study involves a comprehensive review of the literature for evidence on health-related quality of life (HRQoL) and costs. It also attempts a qualitative comparison with estimates of HRQoL for the general population and national healthcare expenditure to illustrate the burden of illness of IPF.

2 Methods

The study followed the PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) guidelines.

2.1 Search Strategy

Two separate systematic reviews were conducted for economic evaluations and HRQoL evidence. Using the Ovid interface, the databases EMBASE, MEDLINE and MEDLINE In Process were searched for relevant studies. Search terms included disease-specific, economic or cost, and HRQoL keywords such as 'idiopathic AND pulmonary AND fibrosis', 'fibrosing alveolitis', 'interstitial pneumonia', 'costs and cost analysis' and 'health care costs', 'HRQoL', 'EQ-5D'.[2]

[1] Nintedanib was also approved in Japan, Canada, Switzerland and many other countries.

[2] For details on the search strings see the electronic supplementary material.

A review of HRQoL was conducted in August 2014 for the development of an economic analysis [25]. All the relevant records from the 2014 review were retrieved and the searches were updated from January 2014 to April 2017.

The economic data search was conducted from database origins to April 2017.

All references were imported into Endnote and duplicate citations were removed.

2.2 Study Selection

A review protocol with inclusion and exclusion criteria was developed at the outset of the study. The inclusion criteria were for adult patients with IPF without any restrictions on the therapy received. Other criteria included the reporting of unit costs, resource use, and HRQoL measures. To increase homogeneity in the study population characteristics, we excluded records that reported costs of diagnosis of interstitial lung disease (ILD).

The protocol was modified during the study to exclude abstract-only records published before 2015 (most often conference proceedings). Those records rarely provided sufficient information on methods and results that could be useful in our study and in general lack the scrutiny of full journal articles. Nevertheless, more recent records (post-2014) were included in our study, as we assumed that at the time of our search they were in development to a manuscript.

Screening of records was conducted in two phases (title/abstract and full-text). One experienced reviewer covered each dataset of records for economic evaluations and HRQoL evidence (EW and KV, respectively). A quarter of the records were screened independently by a second reviewer (AD, LC). If the decision for inclusion or exclusion was different in more than 10%, the full set of records were reviewed again. Because of a $>10\%$ disagreement in the HRQoL dataset, all records were screened in a double-blind manner. The bibliography of another literature review study [26] was used to validate our findings.

2.3 Data Extraction and Analysis

Key pieces of information from the selected studies were extracted in piloted tables by three experienced researchers (EW, KV, LC). A quality check of the data extraction was done by AD. The tables were different for HRQoL and economic evidence. Given the heterogeneity of the economic evidence, we later separated studies that reported healthcare resource use or costs from economic evaluations (cost-effectiveness or budget impact analyses).

3 Results

The database searches identified a total of 3241 records. After removing duplicate records, 2496 abstracts were screened against the eligibility criteria. Twelve additional records were identified via bibliography searches.

A total of 127 publications were included in the qualitative analysis, referring to 66 HRQoL and 28 economic studies. The economic studies were further categorised, with 18 reporting resource use or costs and 10 reporting on cost-effectiveness or budget impact analyses. The overall breakdown of the screening process in the reviews is presented in a PRISMA flow diagram (Fig. 1).

The studies on HRQoL increased over time with almost half conducted and published in the 3.5 years between 2014 and 2017 (see Fig. 2).[3] We did not identify any cost or economic evaluation studies conducted before 2010, while more than half of the cost studies were published in the last 3 years.

In terms of geographic regions, the majority of the studies were conducted in Europe and North America (USA and Canada) (Fig. 3). The most studied country was the USA with 13 HRQoL [27–40] and eight economic evidence publications [41–48]. From low income and lower middle income countries (using the World Bank definition [49]) we identified two studies on HRQoL from Egypt [50, 51] and one from India [52]. From east Asia the predominant country was Japan with nine HRQoL studies [53–61]; one study was identified from China (HRQoL) [62] and one from Korea (costs) [63]. In the HRQoL dataset, for a number of studies we did not identify a clear country of origin [64–67].

3.1 Health-Related Quality of Life Evidence

A total of 66 studies were identified (33 in the pre-2014 analysis and 33 post-2014) with HRQoL data in IPF populations. Details of the study location, the population, the HRQoL assessment tools used, and the time points, as well as the sources of funding, are presented in Table 1.

In all studies, apart from Jastrzebski et al. [69], the population mean age was over 50 years old, with the average age around 65–70 years old. The study populations were predominantly male with the exception of three studies reporting a higher proportion of female [32, 51] or an equal male/female ratio [30].

The majority of the studies used the disease-specific HRQoL instrument, St. George's Respiratory Questionnaire (SGRQ), reported in 41 studies. Most of the studies measuring HRQoL with the SGRQ reported results for the

[3] Note that searches were conducted in April of 2017; hence, only one quarter of the last year contributed to our results.

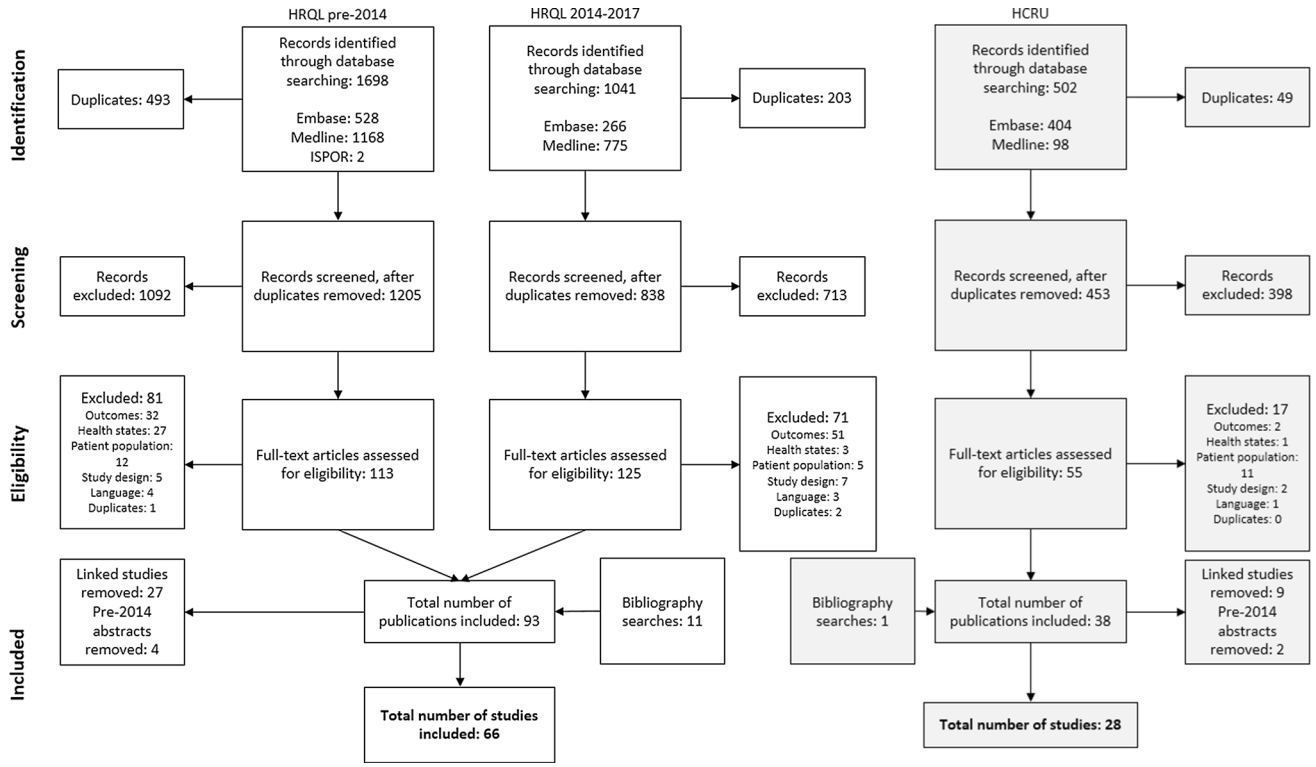

Fig. 1 PRISMA flowchart. *HRQL* health-related quality of life, *HCRU* healthcare resource use

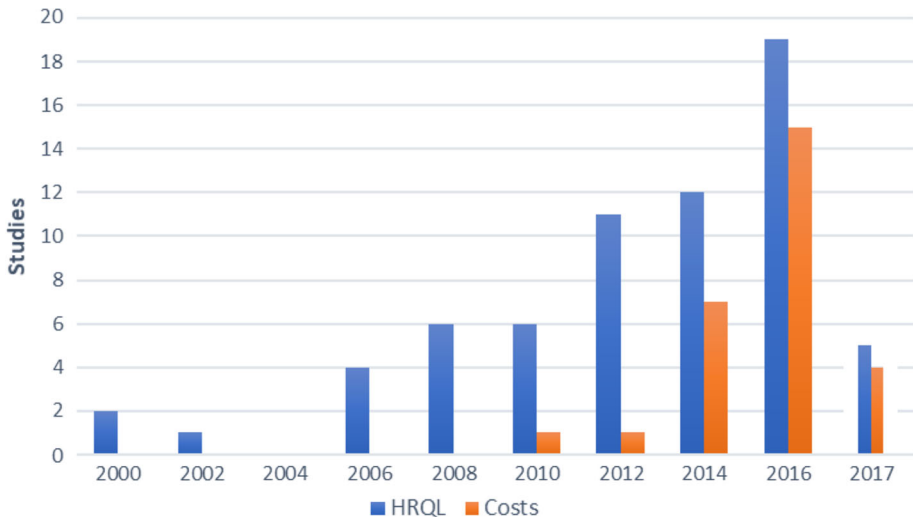

Fig. 2 Summary of studies by publication date. *HRQL* health-related quality of life

three categories: symptoms, impact and activity; in addition to the total score. Despite the development and validation of an IPF-specific version of the SGRQ, the SGRQ-I [70], most investigators, apart from Gaunaurd et al. [28, 71, 72], continue to use the original version.

In addition, six studies reported other disease-specific HRQoL scores such as A Tool to Assess Quality of life in IPF (ATAQ-IPF) [37] or the King's Brief Interstitial Lung Disease (K-BILD) [73]. The 36-Item Short Form Survey (SF-36) was reported in 26 studies, the EuroQol 5-level questionnaire (EQ-5D) in four studies [39, 40, 67, 74, 75], the SF-12 in two studies and one Canadian study reported Health Utilities Index Mark 2 (HUI2) scores. One study was assessing the mapping of SGRQ data to EQ-5D [76] and another study provided a mapping algorithm from SGRQ data to SF-36 [77]. Further, EQ-5D estimates from phase III trials with nintedanib in IPF (INPULSIS® I and II) were available from an economic evaluation identified during the economic data search [25].

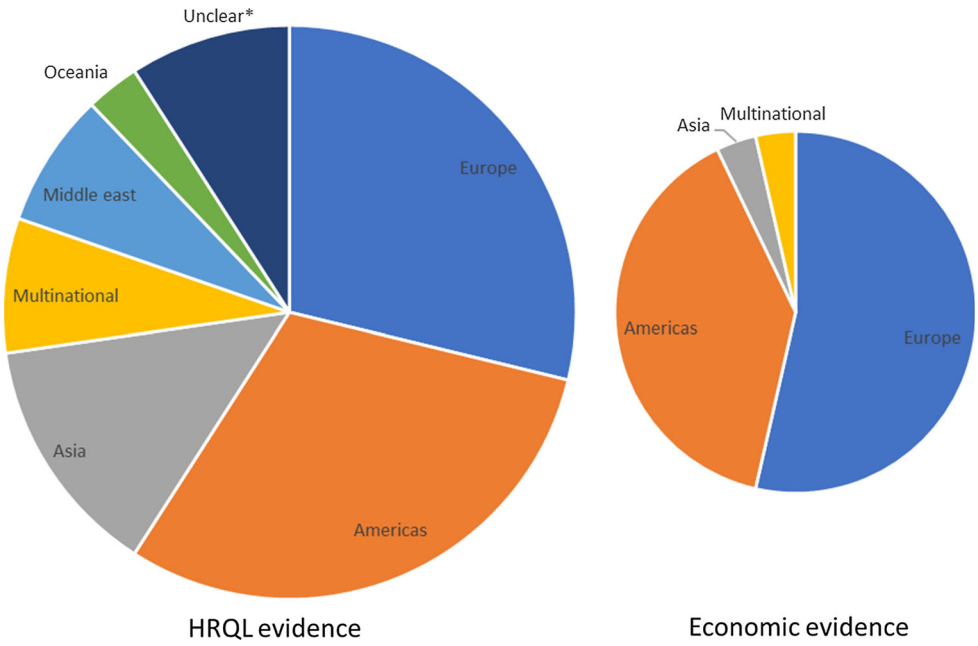

Fig. 3 Regional distribution of identified studies. *HRQL* health-related quality of life. Asterisk indicates the location was not clearly reported in the study

Table 2 reports on a subsection of the studies we found that included HRQoL values based on multi-attribute preference-based measures (EQ-5D and HUI2). We obtained population reference scores for EQ VAS and EQ-5D from a survey conducted across 24 countries [78]. The survey presented scores by age and we selected the 65–74-year age category as the most representative of the IPF studies that we are using in our comparison. To obtain a reference for HUI2 scores, we looked at the US National Health Measurement Study (NHMS) using the scores for ages 65–74 years [79].

Overall, the HRQoL was found to be lower for patients with IPF compared with the general population (Fig. 4). In the German registry, INSIGHTS-IPF, the EQ VAS of the patients with IPF, was about 9 points lower on the scale compared with the population reference data [80–84]. The difference in the EQ-5D index score was 0.223 lower than the reference. The incremental difference between patients with IPF and the population reference is smaller in the US study STEP-IPF: around 7.5 points on EQ VAS and around 0.1 on EQ-5D index scores [67]. Furthermore, in the study by Rinciog et al. [25], the reported difference in EQ-5D index score ranges from a category with relatively good lung function (forced vital capacity [FVC] > 90% predicted: 0.84) to very poor (FVC < 50% predicted: 0.67).

On the HUI2 instrument, the IPF population utility estimates were substantially lower than those measured on the EQ-5D scale, both for the first year with IPF (0.585) and the fourth year (0.432) [12]. However, some of the difference with the reference scores may be attributed to country variations (US data were used for HUI2 reference).

Regarding other multi-attribute instruments, eight studies reported the average score or the mental and physical component scores (MCS and PCS) of SF-36 [27, 29, 34, 35, 39, 40, 67, 69, 85, 86]. One study reported an SF-36 score of 32 ± 11.4 for severe IPF (defined as diffusing capacity of the lungs for carbon monoxide [DLCO] < 30%) and 59.1 ± 17.8 for patients with mild-to-moderate IPF (DLCO > 30%) [27]. King et al. reported the SF-36 score of 45.7 for placebo and 45.2 for people treated with bonsentan [86]. At baseline, SF-36 PCS scores varied between 26.0 ± 8.0 [85] to 40.6 ± 9.3 [40], with an average value of 35 and SF-36 MCS ranging from 42 [69] to 55.7 ± 7.4 [40] with an average value of 48. The 17 remaining studies detailed the SF-36 results by questionnaire items (physical functioning, social functioning, mental health, role limitations due to physical problems, role limitations due to emotional problems, vitality, bodily pain, and general health perceptions).

3.2 Cost and Healthcare Resource Use Evidence

A total of 18 studies were identified with HCRU and cost evidence (Table 3). The majority were retrospective cohort analyses of claims data. Three studies were based on a synthesis of HCRU and national costs or tariffs [87–89]. One study was based on randomised clinical trial evidence [90] and one study was based on clinical expert opinion [91].

The most common reported resource or cost was hospitalisation (all-cause and/or respiratory-related), emergency room visits, and acute IPF exacerbation events. The majority of the studies [14] reported costs alongside

Table 1 Summary of HRQoL evidence

Study	Country	Population			Assessment tools	Time point	Sources of funding
		No. of participants (control)	Mean age of cohort (control)	Male gender (control)			
Alhamad [122]	Saudi Arabia	PFN: 33 (25)	PFN: 63.3 ± 13.3 (62.4 ± 15.1)	PFN: 67% (44%)	Arabic version of SF-36	Baseline and change during follow up	Actelion Pharmaceuticals Ltd.
Antoniou et al. [68]	Greece	IFNγ 1b: 32 Colchicine: 18	IFNγ 1b: 66 (range 54–85) Colchicine: 69 (range 42–82)	IFNγ 1b 91% Colchicine 72%	SGRQ	Change before and after 12 months of treatment	Boehringer Ingelheim Hellas and Society for Pulmonary and Intensive Care Research in the district of East Macedonia and Thrace
Baddini Martinez et al. [123]	Brazil	30[a] Grade 3: 17 Grade 4: 17 Grade 5: 15	58.6 ± 2.0	60%	SF-36	Cross-sectional study	NR
Bahmer et al. [124]	Germany	48	67.1 ± 7.5	75%	SF-12 SGRQ	Baseline	Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen
Bors et al. [27]	USA	46	Severe IPF: 69 (52–79) Mild-moderate IPF: 63 (43–83)	Severe IPF: 58.3% Mild-moderate IPF: 64.7%	SF-36	Baseline	University of Minnesota
Crooks et al. [125]	UK	27[a]	NR	NR	SGRQ	Baseline (assumed)[a]	Hull York Medical School and Hull and East Yorkshire Hospitals NHS Trust
De Vries et al. [126]	The Netherlands	10	61.1 ± 11.6	40%	SGRQ WHOQOL-100	Baseline	NR
Dowman et al. [127, 128]	Australia	Exercise: 32 (29)	Exercise: 70 (73)	Exercise: 66% (69%)	SGRQ-1	Baseline values and change from baseline at 9 weeks and 6 months	ATS Foundation/Pulmonary, Fibrosis Foundation, National Health and Medical Research Council, Eirene Lucas Foundation and Institute of Breathing and Sleep
Elfferich et al. [129]	The Netherlands	IPF: 49 (3678)	IPF: 63.1 ± 11.8 Control: NR	IPF: 62.5% Control: NR	WHOQOL-BREF	Baseline	NR
Fell et al. [12]	Canada	NR	NR	NR	HUI2	1st year 4th year	InterMune Canada Inc.
Ferrara et al. [73]	Sweden	71	70 (range 47–86)	70.40%	K-BILD	Baseline	Swedish Heart and Lung Foundation, Karolinska University Hospital, Karolinska Institutet, Quality-Registry-Centre Stockholm, Boehringer Ingelheim, Intermune/Roche

Table 1 continued

Study	Country	Population			Assessment tools	Time point	Sources of funding
		No. of participants (control)	Mean age of cohort (control)	Male gender (control)			
Freemantle et al. [76]	England and Wales	181	NR	NR	SGRQ mapped to EQ-5D-3L	NA	NR
Furukawa et al. [53]	Japan	182	65.6 ± 8.0	85.20%	SGRQ	Baseline	No funding
Gaunaurd et al. [28, 71, 72]	USA	Rehabilitation: 11 (10)	71 ± 6 (66 ± 7)	NR	SGRQ-I	Baseline Change at 3 months	NR
Glaspole et al. [130]	Australia	516	71.3 ± 8.6	67.30%	SGRQ	Baseline	Australian IPF Registry
Richeldi et al. [25, 110–121][b]	International	NDB: 723 (508)	NR	NDB: 79.1% PBO: 78.1%	SGRQ	Baseline Week 52	TOMORROW and INPULSIS trials funded by Boehringer Ingelheim
Han et al. [33]	USA	221	Average male age 63.3 ± 8.2 Average female age 62.3 ± 9.9	66.50%	SF-12, SGRQ	Cross-sectional study	Lung Tissue Research Consortium
Horton et al. [38]	USA	23	67.6	78.3%	SGRQ	Baseline and 12 weeks	Celgene Corporation
Jarosch et al. [64]	Unclear	33	68 ± 9 (65 ± 10)	NR	SF-36 mental score	Baseline and change at 6 weeks	NR
Jastrzebski et al. [69]	Poland	16	48.3	69%	SF-36	Cross-sectional study	NR
Jo et al. [131]	Australia	647	70.9 ± 8.5	67.7%	SGRQ	Baseline	NR
Jones et al. [132]	UK	27 (30)	71.7 ± 7 (65.6 ± 5.3)	63% Control 70%	VAS, LCQ	Unclear	No funding
Key et al. [133]	UK	19	70.8 ± 8.6	73.70%	VAS, LCQ	Two assessments in 24 hours	No funding
King et al. [77, 86, 134]	International	Bosentan: 71 PBO: (83)	Bosentan: 65.3 ± 8.4 (65.1 ± 9.1)	Bosentan: 69% (76%)	SF-36, SGRQ	Baseline Month 12	Actelion Pharmaceuticals Ltd
King et al. [75]	International	Bosentan: 407 (209)	Bosentan: 63.8 ± 8.4 (63.2 ± 9.1)	Bosentan: 72.7% (63.6%)	SF-36, EQ-5D, EQ-VAS	Baseline Month 12	Actelion Pharmaceuticals Ltd
Kotecha et al. [135]	UK	75	76.4 ± 7.5	77%	SGRQ	Baseline	NR

Table 1 continued

Study	Country	Population			Assessment tools	Time point	Sources of funding
		No. of participants (control)	Mean age of cohort (control)	Male gender (control)			
Kozu et al. [58]	Japan	45	67.5 ± 7.8	82%	SF-36	Baseline Week 8 Month 6	NR
Kozu et al. [59, 136]	Japan	Grade 2: 16 Grade 3: 17 Grade 4: 17 Grade 5: 15	Grade 2: 65.4 ± 7.7 Grade 3: 67.8 ± 7.4 Grade 4: 68.1 ± 7.6 Grade 5: 68.7 ± 7.5	Grade 2: 81.3% Grade 3: 76.5% Grade 4: 64.7% Grade 5: 60%	SGRQ, SF-36	Baseline	No commercial funding
Kramer et al. [65]	Unclear	PRG:15 (13)	PRG: 68.8 ± 6 (65.7 ± 8)	PRG: 61.5 (66.7%)	SGRQ	Baseline 12 weeks	No funding
Kreuter et al. [80–84]	Germany	572	69.4 ± 8.8	77.10%	EQ-5D Index EQ-5D VAS SGRQ	Baseline	NR
Lubin et al. [34]	USA	102	70 ± 8	75%	SF-36 (PCS and MCS)	Baseline	Genentech
Lutogniewska et al. [137]	Poland	IPF: 30	52 ± 10	79%	SF-36 SGRQ	Baseline	NR
Martinez et al. [138]	Brazil	IPF: 34 (34)	58.29 ± 1.87 (58 ± 1.89)	59%	SF-36	Cross-sectional study	NR
Matsuda et al. [54]	Japan	106	67.1 ± 7.5	84.90%	SGRQ	Baseline	Diffuse Lung Disease Research Group from the Ministry of Health, Labor and Welfare. NPO Respiratory Disease Conference
Mermigkis et al. [139]	Greece	12	67.1 ± 7.2	83.30%	SF-36	Baseline Month 1 Month 3 Month 6	NR
Mermigkis et al. [140]	Greece	92	70.3 ± 7.9	68.40%	SF-36	Baseline 1 year	No funding
Mishra et al. [52]	India	IPF: 6 (6)	70.67 ± 11.25	NR	SGRQ	Baseline Week 24	Grants NBA2007 of DBT, IAP001 and CLP 261 of NTRF, India
Morsi et al. [50]	Egypt	36	53.0 ± 13.9	22.20%	SGRQ	Baseline	No funding

Table 1 continued

Study	Country	Population			Assessment tools	Time point	Sources of funding
		No. of participants (control)	Mean age of cohort (control)	Male gender (control)			
Natalini et al. [29]	USA	50	70.8 ± 8.3	78%	SF-36	Baseline	National Centre for Advancing Translational Science
CAPACITY [141]	International	338	66.5 ± 7.6	72.50%	SGRQ	Baseline	InterMune
Nishiyama et al. [61]	Japan	41	64 ± 9	85%	SGRQ	Baseline	NR
Nishiyama et al. [56]	Japan	Rehabilitation group: 13 Control: 15 BIBF1120 50 g × 2 days: 86 BIBF1120 100 g × 2 days: 86 BIBF1120 100 g × 2 days: 85 (85[a])	68.1 ± 8.9 (64.5 ± 8)	92% (60%)	SGRQ	Baseline	Japanese Ministry of Health and Welfare
Nishiyama et al. [57]	Japan	87	66.3 ± 8.2	77%	SGRQ	Baseline	Japanese Ministry of Health and Welfare
Nolan et al. [66]	Unclear	61	70 ± 11	62%	SGRQ	Baseline	NR
Ntolios et al. [142]	Greece	36	69.6 ± 6.2	91.60%	SGRQ	Baseline	NR
Ozalevli et al. [143]	Turkey	17	62.8 ± 8.5	67%	SF-36	Baseline Week 12	NR
Peng et al. [62]	China	68	64 ± 8	79%	Chinese version of SGRQ	Baseline	Institute of Respiratory Diseases
Raghu et al. [35]	USA	ETN: 46 (41)	ETN: 65.2 ± 7.7 (65.1 ± 7.1)	ETN: 76.1% (58.5%)	SF-36 SGRQ	Baseline	NR
Raghu et al. [39, 40]	USA	Combination therapy: 77 (78)	Combination therapy: 68.8 ± 7.3 (67.9 ± 8.1)	Combination therapy: 77% (73%)	SF-36 SGRQ EQ-5D	Baseline Week 60	National Heart, Lung, and Blood Institute (NHLBI) Cowlin Family Fund

Table 1 continued

Study	Country	Population			Assessment tools	Time point	Sources of funding
		No. of participants (control)	Mean age of cohort (control)	Male gender (control)			
Raghu et al. [144]	Belgium, Canada, Germany, the Netherlands and USA	Carlumab 1 mg/kg: 33 Carlumab 5 mg/kg: 32 Carlumab 15 mg/kg: 32 (29)	Carlumab 1 mg/kg: 63.2 ± 9.29 Carlumab 5 mg/kg: 66.3 ± 7.89 Carlumab 15 mg/kg: 65.9 ± 7.38 (64.5 ± 7.26)	Carlumab 1 mg/kg 78.8% Carlumab 5 mg/kg 93.8% Carlumab 15 mg/kg 68.8% (79.3%)	SGRQ	Baseline	NR
Rifaat et al. [51]	Egypt	30	54.4 ± 6.1	26.7%	SGRQ	Baseline 4 weeks 8 weeks	No conflict of interest
Ryerson et al. [30]	USA	54	69.4 ± 10.8	48.00%	SGRQ	Baseline (before PR) After PR (between 6 and 9 weeks) 6 months after PR	No funding
Sharma et al. [31]	USA	IPF: 54 COPD: 456	IPF: 66.3 ± 10.7 (COPD: 66.0 ± 9.1)	No differences in gender	SF-36	Baseline and mean change after PR programme (duration not reported)	NR
Swigris et al. [37]	USA	95	69.3 ± 7.6	82%	ATAQ-IPF	Single assessment	NR
Swigris et al. [36]	USA	21	71.5 ± 7.4	85.70%	SF-36	Single assessment	National Institutes of Health Career Development Award K23 HL092227 Mordecai Palliative Care Research Fund and Colorado Clinical and Translational Science Award 1U11 RR05780
Tomioka et al. [60]	Japan	46	69.9 ± 5.8	70%	SF-36	Baseline and follow-up (median 14 months)	NR
Tomioka et al. [55]	Japan	17	76.5 ± 7.1	88.20%	SF-36	Baseline 3 weeks (post-PR)	No funding
Tzanakis et al. [145]	Greece	IPF patients: 25 (30)	66 ± 11 (63.5 ± 10)	84% (80%)	SGRQ, QWB, HAD	Cross-sectional study	NR

Table 1 continued

Study	Country	Population			Assessment tools	Time point	Sources of funding
		No. of participants (control)	Mean age of cohort (control)	Male gender (control)			
Tzouvelekis et al. [146]	Greece	14	64.4 ± 7	86%	SGRQ	Baseline 6 months post-infusion 12 months post-infusion	Godrej Group Adistem Ltd and the Hellenic National Research Foundation Stem Cell Bank Athens, Greece, Biohellenika SA Thessaloniki Greece
Vainshelboim et al. [147, 148]	Israel	ET: 15 (17)	ET: 68.8 ± 6 (66 ± 9)	ET: 67% (65%)	SGRQ	Baseline Week 12	No funding
Verma et al. [149]	Canada	137	59.4 ± 7.1	65.70%	SF-36 SGRQ	Cross-sectional study	NR
Wuyts et al. [150, 151]	Belgium and Luxemburg	147	68.3 ± 9.2	80%	SGRQ	Baseline	InterMune, Inc.
Yazdani et al. [85]	Canada	53	IPF: 61.0 ± 4.04	72%	SF-36 SGRQ	Baseline 1st post-treatment visit 2nd post-treatment visit	Dolly Roth Memorial Rheumatoid Arthritis Research Fund
Yount et al. [32]	USA	220	61.0 ± 5.6	30.40%	PROMISdyspnea PROMIS-29 ATAQ-IPF (6–30) FACIT cough (0–4)	Baseline	Biogen
Zimmermann et al. [152]	Brazil	20	61.4 ± 10.5	60%	SF-36, SGRQ	Baseline	FAPESP and LIM HC-FMUSP

Table 1 continued

Study	Country	Population			Assessment tools	Time point	Sources of funding
		No. of participants (control)	Mean age of cohort (control)	Male gender (control)			
Zisman et al. [67]	NR	Sildenafil: 89 (91)	Sildenafil: 69.8 ± 8.7 (PBO: 68.2 ± 9.3)	Sildenafil: 84% (80.0%)	SF-36, SGRQ, EQ-5D, EQ-5D VAS	Baseline	NHLBI; the Cowlin Fund at the Chicago Community Trust; Pfizer donated sildenafil and matching placebo and Masimo donated pulse oximeters

ATAQ-IPF A Tool to Assess Quality of life in IPF, *BIBF* Bahrain Institute of Banking and Finance, *COPD* chronic obstructive pulmonary disease, *DBT* Department of biotechnology, *EQ-5D* EuroQol 5-level, *ET* exercise and training, *ETN* etanercept, *FACIT* Functional Assessment of Chronic Illness Therapy, *FAPESP* Fundação de Amparo à Pesquisa do Estado de São Paulo, *HAD* Hospital anxiety and depression scale, *HRQoL* health-related quality of life, *HUI2* Health Utilities Index Mark 2, *IFN* inflixima b, *IPF* idiopathic pulmonary fibrosis, *K-BILD* King's Brief Interstitial Lung Disease, *LIM HC FMUSP* Laboratórios de Investigação Médica do Hospital das Clínicas, *LCQ* Licence Controller Qualification, *MCS* Mental Component Score, *NA* Not applicable, *NDB* nintedanib, *NR* not reported, *NTRF* National Tea Research Foundation, *PBO* placebo, *PCS* Physical Component Score, *PFN* pirfenidone, *PR* pulmonary rehabilitation, *PRG* Pulmonary Rehabilitation Group, *PROMIS* Patient Reported Outcomes Measurement Information System, *QWB* Quality of well-being scale, *SF-12* Short Form-12; *SF-36* Short Form-36, *SGRQ* St George's Questionnaire, *SGRQ-I* IPF-specific version of the SGRQ, *UK* United Kingdom, *USA* United States of America, *VAS* Visual Analogue Scale, *WHQOL-BREF* WHO Quality of Life-BREF

[a] No. of patients assessed

[b] INPULSIS I and II studies also collected EQ-5D available from Rinciog et al. [25] (identified in the economic evaluations)

resource use. Four studies reported only HCRU data [47, 90, 92, 93].

Eight of the studies that reported costs presented estimated total cost per capita [41, 42, 44, 63, 88, 91, 94, 95] (see Table 4). In three US studies the annual total cost of IPF was estimated at around US$20,000 per patient [41, 42, 44]. Controlled for the year the studies were conducted, this estimate was around three times the national per capita health expenditure [96].

In 2012, Collard et al. [42] also presented the total costs per person-year for patients with IPF and a matched control cohort (US$26,378 vs US$14,254). In a different study, published a few years later (2015), Collard et al. [41] showed similar estimates of the difference between patients with IPF and controls (US$20,887 vs US$8932).

In a study from Canada [94], the annual cost per patient with IPF was lower than the US studies [41, 42, 44]. However, in relative terms the study estimated a >3 times greater cost when comparing with the per capita Canadian national heath expenditure.

The annual total cost per patient in Korea [63] was estimated to be $<10\%$ of the cost presented in the American studies [41, 42, 44]. In the same study, the contribution of hospital admission costs to the total healthcare cost was found to be 86.7–88.8%. We also found great disparity in the estimates of the two studies from Spain [91, 97].

An abstract by Hill et al. [88] conducted a bottom-up cost analysis of service provision costs (excluding treatments) in England (NHS) in 2014. They estimated that the actual cost of services was over 40% of the tariff reimbursed by the NHS for each patient with IPF.

From the studies that reported resource use, Wu et al. [93] presented evidence of HCRU in US patients with IPF compared with a matching control cohort (1:3 matching ratio). They found that the mean differences between patients with IPF and control were more pronounced in outpatient hospital visits (7.5 vs 2.7), physician office visits (16 vs 7.8), and oxygen therapies (7.8 vs 0.6). After a multivariate adjustment, the magnitude of the difference was reduced for the outpatient hospital, physician and emergency room visit statistics. Nevertheless, it remained significantly higher for patients with IPF versus non-IPF.

Only five studies reported treatment costs [42, 44, 63, 89, 91]. In Kim et al., treatment costs were between 8–10% of the total costs [63]. However, it was not reported which treatment was considered. In the remaining studies, treatments included corticosteroids, oxygen therapy, azathioprine, cyclophosphamide, *N*-acetylcysteine (NAC), pulmonary rehabilitation therapy and lung transplantation. Of the new treatments, in Morell et al. it was reported that pirfenidone was offered to patients with IPF on compassionate grounds; it is unclear whether the cost of

Table 2 HRQoL burden of IPF

Study	Patient characteristics	HRQoL multi-attribute measurement tool	IPF utility score	Population reference data[a]
INSIGHTS-IPF [80–84]	$N = 572$ patients; 77.1% males; mean age 69.4 ± 8.8 years; disease 2.1 ± 3.3 years; FVC % predicted 72.6 ± 19.2; DLCO % predicted 36.1 ± 17.1	EQ VAS	59.8 ± 19.8	Germany, age 65–74 years: 68.6
		EQ-5D-5L	0.668 ± 0.214[b]	Germany, age 65–74 years: 0.891
BUILD-1 [77, 86, 134]	$N = 407$ patients; 73% males; mean age 65.12 ± 8.93; disease < 3 years; FVC % predicted 66.97 ± 12.17; DLCO % predicted 40.98 ± 10.08	EQ VAS	Placebo: 69.5 ± 19.4 Bosentan: 70.4 ± 18.7	N/A (international study)
		EQ-5D	Placebo: 0.718 ± 0.242 Bosentan: 0.758 ± 0.185	N/A (international study)
STEP-IPF [67]	Placebo $N = 91$ patients; 84% males; mean age 68.20 ± 9.25; disease 1.87 ± 1.93 years, FVC % predicted 58.73 ± 14.12; DLCO % predicted 26.73 ± 6.16	EQ VAS	Baseline: 67.66 ± 16.98 Change at 12 weeks: -1.81 (-5.34 to 1.73)	USA, age 65–74 years: 75.1
		EQ-5D-5L	Baseline: 0.74 ± 0.19 Change at 12 weeks: -0.03 (-0.08 to 0.01)[b]	USA, age 65–74 years: 0.817
	Sildenafil $N = 89$ patients; 86% males; mean age 69.76 ± 8.71; disease 2.03 ± 1.94 years, FVC % predicted 54.89 ± 14.00; DLCO % predicted 25.81 ± 6.03	EQ VAS	Baseline: 66.49 ± 17.45 Change at 12 weeks: 0.48 (-3.10 to 4.06)	USA, age 65–74 years: 75.1
		EQ-5D-5L	Baseline: 0.71 ± 0.24 Change at 12 weeks: -0.01 (-0.06 to 0.03)[b]	USA, age 65–74 years: 0.817
INPULSIS I and II [25]	Placebo $N = 423$ patients; 79% males; mean age 67 ± 7.9 years; disease 1.57 ± 1.31 years; FVC % predicted 79.27 ± 18.22 Nintedanib $N = 638$ patients; 79.5% males; mean age 66.6 ± 8.1 years; disease 1.65 ± 1.36 years; FVC % predicted 79.74 ± 17.57 Both arms were pooled for this analysis	EQ-5D-3L	FVC $\geq 90\%$ 0.84 ± 0.18 FVC 80–89.9% 0.81 ± 0.21 FVC 70–79.9% 0.78 ± 0.22 FVC 60–69.9% 0.77 ± 0.24 FVC 50–59.9% 0.74 ± 0.23 FVC 40–49.9% 0.66 ± 0.26	N/A (international study)

Table 2 continued

Study	Patient characteristics	HRQoL multi-attribute measurement tool	IPF utility score	Population reference data[a]
Fell et al. [12]	Details were not reported (abstract)	HUI2	1st year: 0.585 4th year: 0.432	USA population, age 65–74 years: 0.85

DLCO diffusing capacity of the lungs for carbon monoxide, *EQ-5D* EuroQol 5-level, *FVC* forced vital capacity, *HRQoL* health-related quality of life, *HUI2* Health Utilities Index Mark 2, *IPF* idiopathic pulmonary fibrosis, *N/A* not available, *VAS* Visual Analogue Scale

[a]EQ-5D index population norms (country-specific time trade-off value sets) [78, 79]

[b]The study used the EQ-5D-5L version, which may not be directly comparable to the population reference data

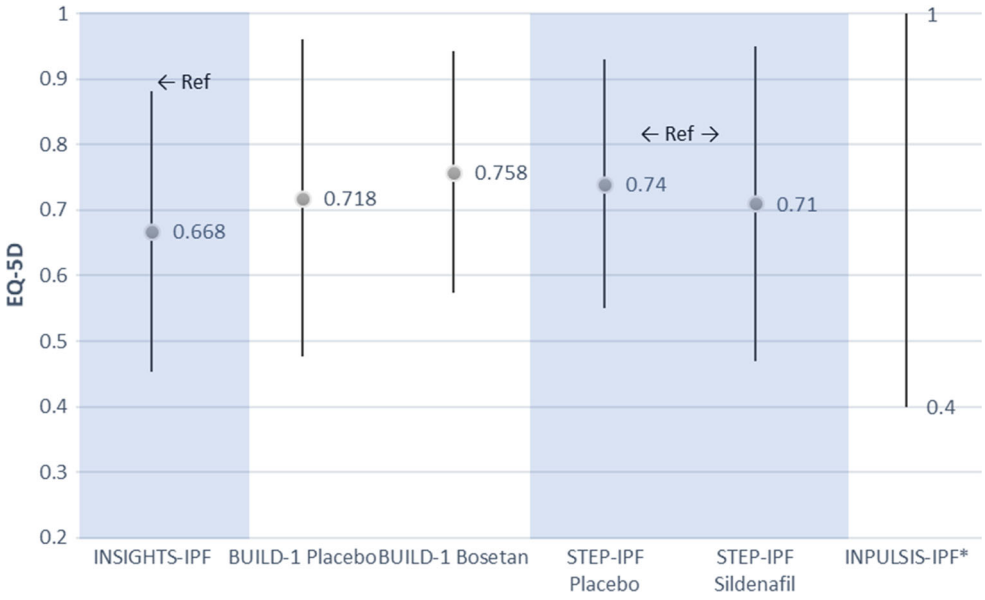

Fig. 4 EuroQol 5-level questionnaire (EQ-5D) in patients with idiopathic pulmonary fibrosis (IPF) compared with the general population (reference). *FVC* forced vital capacity. Asterisk indicates data from by Rinciog et al. were available by FVC% predicted status. The lowest and highest of the available intervals are shown in the figure [25]

pirfenidone contributed to the treatment costs in that study [91].

3.3 Economic Evaluations

Ten studies were identified assessing the cost effectiveness, or budget impact, of specific treatment interventions. Details of the methods and results of the studies are presented in Table 5. Three studies were from the UK [25, 26, 98], while the remaining were from France [99], Greece [100], Italy [101, 102], Spain [103], Mexico [104] and USA [105]. The comparators included triple therapy (azathioprine, NAC and steroids), a combination of triple therapy and a genotypic assay thiopurine *S*-methyltransferase (TPMT), co-trimoxazole, sildenafil, pirfenidone, nintedanib and best supportive care. Only one economic evaluation included lung transplantation as an option for patients [26].

Most studies used a model to synthesise clinical, HRQoL and cost evidence. Moreover, the majority of the analyses used the direct healthcare perspective. Wilson et al. [98] conducted an economic evaluation alongside a multi-centre, randomised, placebo-controlled, double-blind trial of 12 months duration, and reported cost-effectiveness results on both the healthcare direct medical and societal perspectives.

In the economic models, the time horizon ranged between 1, 5 and 30 years, and patient lifetime. A state transition model was used for all papers, and when reported, results were calculated by a cohort analysis. In the long time-horizon models, the cost results varied between US$4000 (£3000) for BSC, US$7000 for NAC and over US$90,000 for new treatments such as pirfenidone and nintedanib. HRQoL benefits ranged between 3 and 4 QALYs. There was a noticeable distinction in the cost effectiveness of old pharmacologic technologies such as triple therapy or NAC, with estimates between US$5000–US$70,000 per QALY, and that of new treatments that exceeded US$100,000 per QALY.

Table 3 Summary of cost and resource use studies

Study	Country	Valuation method	Population			Evidence reported	Sources of funding
			Inclusion criteria	Mean age of cohort (control)	Male gender (control)		
Collard et al. [42]	USA	Retrospective cohort analysis; claims data	Age > 55 years; IPF patients with ≥ 2 claims with a code for idiopathic fibrosing alveolitis (ICD-9 516.3), or 1 claim with ICD-9 516.3 and a subsequent claim with a code for post-inflammatory pulmonary fibrosis (ICD-9 515). Matched control cohort also analysed	74	54.6 (54.6)	Total costs for IPF and control patients. Breakdown of healthcare resource use: hospital admissions, ER, OP, physician visits, oxygen, rehabilitation, monitoring	Actelion Pharmaceuticals Ltd
Collard et al. [41, 153]	USA	Retrospective database analysis; claims data	All patients received Medicare cover between Jan 2000 and Dec 2011. Age > 65 years. At least one claim with ICD-9-CM diagnosis code 516.3	78.5 ± 6.9 (78.4 ± 6.9)	43.3 (43.1)	Total costs for IPF and control, including cost breakdown. HCRU breakdown: all-cause hospitalisation, all-cause ER visits, all-cause outpatient visits, physician office visits, respiratory related visits, oxygen therapy, pulmonary rehab, monitoring	Biogen
Cottin et al. [154, 155]	France	Retrospective observational study	Patients with a first hospitalization for IPF (ICD-10 code: J841) and aged ≥ 50 y	75.4 ± 10.3	56%	Mean total cost of hospitalisations, specific cost drivers, acute exacerbations, cardiac events, acute respiratory infections, in-hospital mortality rate, arterial thrombosis, palliative care and associated costs	NR
Diamantopoulos et al. [90]	International	Post-hoc clinical trial data analysis	Patients from the INPULSIS trial	NR	NR	The impact on a patient's hospitalisation from changes in disease status (FVC% predicted) and exacerbations	Boehringer Ingelheim
Goode et al. [87]	UK	Cost analysis based on MRU	Patients with IPF	NR	NR	Cost associated with diagnosing IPF, including specific test costs and overall total cost	Boehringer Ingelheim UK
Hill et al. [88]	UK	Cost analysis based on MRU	NR (abstract): evidence taken from IPF services	NR	NR	Estimated mean cost per patient for first year of diagnosis, management and monitoring	NR

Table 3 continued

Study	Country	Valuation method	Population			Evidence reported	Sources of funding
			Inclusion criteria	Mean age of cohort (control)	Male gender (control)		
Kim et al. [63, 156]	Korea	Retrospective database analysis; claims data	Patients with IPF who had made ≥ 2 claims per year under the K-J84.18 code (IPF) of the medical care system, using the KCD-6 codes	Mean age for males: 2009: 66.0 ± 13.1 years 2010: 66.9 ± 12.5 years 2011: 67.0 ± 12.8 years 2012: 67.9 ± 12.1 years 2013: 68 ± 12.1	2009: 60.7 2010: 61.1 2011: 62.2 2012: 62.5 2013: 62.9	Total costs for IPF patients per year, per person per year, and per unit/item per year. HCRU breakdown: all-cause hospitalisation, LOS, all-cause ER visits, intensive care, monitoring	NR
Mittmann et al. [94]	Canada	Retrospective, longitudinal cohort study; chart review analysis	Adults with a confirmed diagnosis of IPF and a minimum of one respirologist visit	71.3 (range 39–89)	66.7%	Overall cost, mean cost per patient, 30-day cost per patient	NR
Mooney et al. [43, 157]	USA	Retrospective cross-sectional study; claims data	Patients with ≥ 1 IP claim of IPF (ICD-9-CM code 516.3) between 2009 and 2011. Principal diagnosis of respiratory disease (ICD-CM 460-519)	Overall: 70 ± 0.32[a]	Overall: 50.9% [a]	All-cause hospitalisation, total admission costs	Genentech and Boehringer Ingelheim Pharmaceuticals
Morell et al. [91]	Spain	Three-round Delphi consensus panel	Patients with IPF	NR	NR	Total costs, including specific unit costs. HCRU breakdown: Numbers of patients with IPF and their resource use, including specific drug, exacerbations, IPF-related hospitalisations, ICU, IPF-related outpatient visits, oxygen, pulmonary rehab, lung transplant, AEs, palliative care and monitoring	Boehringer Ingelheim
Nasr et al. [89]	UK	Cost analysis based on 11 different sources	Adults with IPF	NR	NR	Average annual cost of NAC	NR

Table 3 continued

Study	Country	Valuation method	Population			Evidence reported	Sources of funding
			Inclusion criteria	Mean age of cohort (control)	Male gender (control)		
Navaratnam et al. [158]	UK	Retrospective database analysis	Patients with fibrotic lung disease of unknown origin with ICD codes J84.1 and J84.9; study looks at the burden of IPF	49–71[b]	NR	Cost of inpatient bed days, hospital admission rates, LOS, cost of hospital admission	Dr Navaratnam: research grant from the Medical Research Council. Dr Hubbard: the GlaxoSmithKline/ British Lung Foundation chair of Epidemiological Respiratory Research
Pedraza-Serrano et al. [97]	Spain	Retrospective descriptive epidemiological study; administrative data	All patients hospitalised for IPF (ICD-9-CM 561.3)	73.11 ± 12.28[c]	57.35%[c]	Total costs, all-cause hospitalisation, lung transplant and monitoring	URJC–Banco Santander to the Grupo de Excelencia Investigadora ITPSE
Raimundo et al. [44, 159]	USA	Retrospective database analysis; claims data	Patients with ≥ 1 inpatient claim or 2 outpatient claims with IPF as one of the listed diagnosis codes (ICD-9-CM 516.3) in 1 year excluding other interstitial lung disease diagnosis	Ages reported for years 2009–2011 2009: 69.8 ± 11.1 2010: 70.0 ± 11.4 2011: 71.3 ± 10.6	48.10%	Total costs, hospitalisation, ER and OP visits, (reported for all-cause and IPF related). As well, oxygen, pulmonary rehab, lung transplant and monitoring	Genentech Inc.
Sharif et al. [45]	USA	Retrospective database analysis	Patients categorized into IPF group from patients with acute exacerbation of COPD (ICD-9 491.21), rheumatoid lung disease, systemic sclerosis interstitial lung disease, other CTD-ILDs and IPF (ICD-9 of 516.31)	NR	NR	Total cost of hospitalisation, total costs per day, LOS, ICU days	No funding
Yu et al. [46]	USA	Retrospective database analysis; claims data	Adult patients with a new IPF diagnosis (≥ 2 claims of idiopathic interstitial pneumonia (ICD-9-CM 516.3) OR one claim of 516.3 and one claim of post-inflammatory pulmonary fibrosis (ICD-9-CM 515)	66	57%	Comorbidities, mortality rates, hospital admissions, LOS, ER admissions, outpatient admissions, office visits, oxygen, pulmonary lung biopsy procedures, and monitoring	Boehringer Ingelheim Pharmaceuticals, Inc.

Table 3 continued

Study	Country	Valuation method	Population			Evidence reported	Sources of funding
			Inclusion criteria	Mean age of cohort (control)	Male gender (control)		
Yu et al. [47]	USA	Retrospective chart review	Patients aged ≥ 40 years, diagnosed with IPF (diagnosis between Jan 2011 and June 2013)	With early acute exacerbation: 59.0 ± 10.8 Without: 61.4 ± 10.7	With early acute exacerbation: 63.9% Without: 69.1%	Acute exacerbations, IPF-related hospitalisations, ER visits, OP visits, urgent care visits	Boehringer Ingelheim
Yu et al. [48, 93]	USA	Retrospective database analysis; claims data	Adults newly diagnosed with IPF between Jan 2007 and Dec 2011	71.5 ± 12.7	54%	Total IPF-related hospitalisation costs, all-cause hospitalizations, IPF-related hospitalizations, possible acute exacerbations requiring hospitalization, and possible acute exacerbations not requiring hospitalization	Boehringer Ingelheim

AE adverse event, *COPD* chronic obstructive pulmonary disease, *CTD-ILD* connective tissue diseases–idiopathic lung disease, *ER* emergency room, *FVC* forced vital capacity, *HCRU* healthcare resource use, *ICD-9-CM* International Classification of Diseases, ninth revision, clinical modification, *ICU* intensive care unit, *IP* in-patient, *IPF* idiopathic pulmonary fibrosis, *LOS* length of stay, *MRU* medical resource use, *NAC* *n*-acetylcysteine, *NR* not reported, *OP* outpatient

[a]Mean age and gender given for years 2009–2011, results reported are mean over 3 years

[b]Navaratnam [158] report mean age at admission for groups J84.1 and J84.9 for years 1998–2010

[c]Ages and genders for years 2004–13 reported

Table 4 Cost burden of IPF

Study	Cost year	Currency	IPF annual cost per patient (USD conversion for study year)	National per capita health expenditure	IPF/NHE
Collard et al. [42]	NR	USD	$26,378	USA 2012: $8423	3.13
Collard et al. [41, 153]	2012	USD	One year before index quarter: $10,124 One year after: $20,887	USA 2012: $8423	2.48
Hill et al. [88]	NR	GBP	£1414[a] ($2259)	UK 2014: $3989	0.57
Kim et al. [63, 156]	NR	USD	$1376–$1744	Korea 2016: $2729	0.64
Mittmann et al. [94]	2014	CAD	$19,421 ± $18,961 ($17,444 ± $17,031)	Canada 2014: $4502	3.87
Morell et al. [91]	2013	EUR	€26,435.1 ($35,373)	Spain 2013: $2941	12.03
Pedraza-Serrano et al. [97]	NR	EUR	€5249.35 ± €7737.83 ($5584 ± $8232)	Spain 2016: $3248	1.72
Raimundo et al. [44, 159]	2011	USD	$21,732[b]	USA 2011: $8145	2.67

CAD Canadian Dollars, *EUR* Euros, *GBP* Great British Pounds, *IPF* idiopathic pulmonary fibrosis, *NHE* national per capita health expenditure, *NR* not reported, *USD* US Dollars

[a]Estimated annual cost of service provisions in England. No treatment costs were included

[b]36.6% of $59,379 per patient in 2011

4 Discussion

This was a review of HRQoL, resource use, costs and treatment cost-effectiveness studies conducted over the last 20 years in many countries, and with a variety of objectives, sources of data, and methodologies. As such, it is difficult to express with one coherent estimate the burden of illness of IPF. Nevertheless, several trends appeared in both quality of life and costs.

As with other respiratory conditions, the impact of IPF is not only limited to a worsening of the patient's breathing function. It has wider consequences for HRQoL including physical (body weight loss, fatigue, clubbing) and social ones (recreational activities, relationships etc.). When reviewing the HRQoL evidence, this review reported on most instruments used in the literature, but focused on generic preference-based measures (such as EQ-5D) to quantify the burden of the disease. By using EQ-5D it is possible to make a comparison between the HRQoL levels with the condition versus the general population, and a comparison across other non-respiratory diseases. Furthermore, EQ-5D is increasingly used in health economic evaluations to calculate quality-adjusted life-years (QALYs), and this work presents a comprehensive review of the available evidence.

Despite the regional differences, there was some agreement between study estimates on the absolute level of HRQoL for patients with IPF; in EQ-5D, scores varied between 0.67 (± 0.242) [67] and 0.8 (± 0.2) [106]. To put this in context, the EQ-5D of patients with arthritis/rheumatism/fibrositis was reported to be 0.597 (CI 0.584–0.609; $N = 4145$), with hypertension/high blood pressure 0.777 (CI 0.765–0.788; $N = 3172$) and with asthma 0.797 (CI 0.779–0.814; $N = 2452$) [107, 108]. In the studies analysed, the decrement in HRQoL for patients with IPF compared with the reference population statistics was between 0.1 and 0.2 points in the EQ-5D.

With regards to costs, three US studies produced comparable estimates of costs per patient around US$20,000 [41, 42, 44]. After adjustments for the study years and currency, the suggested annual per capita cost of IPF patients in North America was estimated between 2.5–3.5 times the national health care expenditure.

We observed discrepancy in the estimates coming from two Spanish studies. This is probably attributed to the methods used. Pedraza-Serrano et al. [97] used data from a Spanish National Hospital Database (CMBD, Conjunto Mínimo Básico de Datos) and conducted a retrospective, descriptive, epidemiological study. Morell et al. [91] took a different approach by synthesising expert opinion from 15 clinicians with unit costs from national formularies. Moreover, Morell et al. [91] included treatments costs, although treatment allocation was not reported. The two estimates are very different to values from the other countries (in absolute and relative terms), which makes it very challenging to select the most accurate. The study by Pedraza-Serrano et al. [97] follows the general trend of a higher per annum cost than the national health expenditure.

Among the cost evidence identified in the literature, we emphasised the existence of matched control cohort studies [41, 42, 93]. These papers provided a direct comparison of the excess costs and resource use of IPF patients versus a

Table 5 Summary of economic evaluations

Study	Country	Cost year	Currency	Type of economic evaluation	Population	Time horizon	Comparators	Effectiveness	Costs	Cost effectiveness	Sources of funding
Benard et al. [99]	France	NR	Euros	Cost utility analysis	Adults with IPF	Cohort lifetime	Pirfenidone Nintedanib	NR (Abstract) NR (Abstract)	€82,667 €76,668	Nintedanib 57.1% chance of being more effective and 76.2% chance of being cheaper than pirfenidone	Boehringer Ingelheim
Capano et al. [101]	Italy	NR	Euros	Cost-effectiveness analysis	Adults with IPF	1 year	Pirfenidone	NR (Abstract)	Budget impact: €11,121,549	59,712 €/ ΔFVC%	NR
Hagaman et al. [105]	USA	2007	USD	Model-based cost-utility analysis	IPF patients stratified by TPMT prevalence: normal (high) 87.6% 85.6–90%, intermediate 11.9% 7.8–13.5%, and low (absent) 0.5% 0–3%	1 year	Conservative therapy Azathioprine, NAC and steroids +TPMT assay	2.50 QALYs 2.61 QALYs 2.62 QALYs	$9969 $15,802 $15,818	TPMT + triple vs conservative $49,156 per QALY. TPMT vs triple $29,662 per QALY gained	NR
Loveman et al. [26, 160]	UK	NR	GBP	Model-based cost-effectiveness analysis	Patients with IPF	30 years	BSC Azathioprine and prednisolone NAC triple therapy Inhaled NAC Sildenafil Pirfenidone Nintedanib	2.98 2.66 3.03 3.37 3.11 3.34 4.01	£3084 £4313 £5021 £5029 £12,008 £70,118 £139,613	Reference Dominated by BSC £41,811 per QALY gained £5037 per QALY gained £68,116 per QALY gained £190,146 per QALY gained £132,658 per QALY gained	NIHR

Table 5 continued

Study	Country	Cost year	Currency	Type of economic evaluation	Population	Time horizon	Comparators	Effectiveness	Costs	Cost effectiveness	Sources of funding
Pozo and Paladio-Hernandez [104]	Mexico	NR	Costs converted to USD from MXN	Model-based cost-effectiveness analysis	NR: study looks at treating IPF	1 year	Triple therapy Pirfenidone	– 14.3 exacerbations avoided with pirfenidone	$154,582 $121,293	NR	NR
Ravasio et al. [102]	Italy	NR	Euros	Model-based cost-utility analysis	Adult patients with mild/moderate IPF	Cohort lifetime	BSC Nintedanib Pirfenidone	NR NR Incremental effectiveness to BSC: +2.42 LYs; +1.95 QALYs and to nintedanib: +1.30 LYs; +1.04 QALYs	€26,570 €93,948 €102,504	€31,360/LY and €39,012/QALY versus BSC and €6460/LY and €8199/QALY vs nintedanib	NR
Rinciog et al. [25]	UK	2012/2013	GBP	Model-based cost-effectiveness analysis	Adults with IPF	Cohort lifetime	BSC NAC Pirfenidone Nintedanib	3.0999 QALYs NR 3.4509 QALYs 3.5013 QALYs	£20,029 £80,474 £78,351	Reference Dominated by BSC £172,198/QALY vs BSC £145,310/QALY vs BSC	Boehringer Ingelheim
Soulard and Crespo [103]	Spain	2016	Euros	Model based cost-effectiveness analysis	Adult patients with IPF (hypothetical cohort)	Cohort lifetime	Pirfenidone Nintedanib	3.62 QALYs 3.66 QALYs	NR Nintedanib was €6854 less costly compared with pirfenidone	Nintedanib dominated pirfenidone	NR
Tritaki et al. [100]	Greece	2016–2020	Euros	Budget impact model	Adults with IPF. Clinical data were obtained from clinical trials INPULSIS I and II for nintedanib, CAPACITY for pirfenidone	5 years	Pirfenidone Nintedanib	NR Reduction of acute exacerbations 2016: − 5 events 2010: − 18 events	NR Net budget impact of nintedanib at 2016 = €2,088,281	NR	NR

Table 5 continued

Study	Country	Cost year	Currency	Type of economic evaluation	Population	Time horizon	Comparators	Effectiveness	Costs	Cost effectiveness	Sources of funding
Wilson et al. [98]	UK	2011/2012	GBP	Cost-utility analysis based on an RCT	Patients with a diagnosis of fibrotic IIP including either IPF6 or fibrotic non-specific interstitial pneumonia, aged ≥ 40 y, MRC dyspnoea score of ≥ 2 whose treatment regimens had remained unchanged for ≥ 6 weeks	1 year	Placebo Co-trimoxazole	ITT NHS: 0.539 QALYs ITT Societal: 0.539 QALYs PP NHS: 0.527 QALYs PP Societal: 0.527 QALYs ITT NHS: 0.571 QALYs ITT Societal: 0.590 QALYs PP NHS: 0.571 QALYs PP Societal: 0.584 QALYs	ITT NHS: £3136 ITT Societal: £17,210 PP NHS: £3161 PP Societal: £18,587 ITT NHS: £3186 ITT Societal: £16,240 PP NHS: £3205 PP Societal: £16,434	*Unadjusted* ITT NHS: ICER £1567 ITT Societal: active dominant PP NHS: £993 PP Societal: active dominant *Adjusted for baseline utility and costs* ITT NHS: ICER £6818 ITT Societal: ICER £22,012 PP NHS: £4849 PP Societal: £11,400	East Anglia Thoracic Society, NIHR for Patient Benefit (RfPB) Programme, NIHR Cambridge BRC, Boehringer Ingelheim non-commercial educational grant

BSC best supportive care, *FVC* forced vital capacity, *GBP* Great British Pound, *ICER* incremental cost effectiveness ratio, *IIP* idiopathic interstitial pneumonia, *IPF* idiopathic pulmonary fibrosis, IPP idiopathic interstitial pneumonia, *ITT* intention to treat, *LY* life-year, *MRC* Medical Research Council, *MXN* Mexican Pesos, *NAC* N-acetylcysteine, *NHS* National Health Service England, *NIHR* National Institute for Health Research, *NR* not reported, *PP* prescription prepayment, *QALY* quality-adjusted life-years, *RCT* randomised controlled trial, *TPMT* thiopurine S-methyltransferase, *UK* United Kingdom, *USA* United States of America, *USD* United States Dollars

reference population. Given that these studies were large in sample size and from a contemporary (2012 and 2015) and generalisable database, they produced relevant estimates for the cost burden of illness of IPF. Therefore, we recommend the use of control or reference cohorts when conducting cost analyses as it provides the relevant benchmark for comparison with the general population.

Two studies also suggested a strong correlation between acute exacerbations of IPF and other external conditions such as seasonality. Collard et al. [41] reported that acute exacerbations of IPF become more frequent in spring and winter. Kim et al. [63] highlighted spring as the season with most events, and linked that to the yellow dust phenomena occurring during that period in Korea, where this study was conducted.

The reader should note the relevance of national guidelines and prescription rules when comparing costs from different countries. Countries with a single (public) payer system, like the UK, have different practices and prescription rules to multiple-payer systems such as Germany in Europe or the US. It is also relevant to consider that some countries may have delayed access to new treatments; for instance, Australia only gained access to new anti-fibrotic agents in 2017, while Europe and the US has had access since 2010–2015.

The evidence on treatment economic evaluations was sparser. The cross-comparison of cost-effectiveness analyses is often hindered by different methodologies, time horizons, approaches in the presentation of the results and many other factors. On this occasion, an additional challenge was that most studies were published only as conference abstracts and, as such, provided little information on their methods and results. This made any comparison or synthesis of cost-effectiveness estimates very difficult.

One omission of our cost estimates is related to the diagnosis of IPF. The diagnostic procedures are largely in common with other ILDs and in most diagnostic cost studies evidence was presented from a heterogenous cohort that included patients with IPF as a subgroup [87, 109]. To include only studies that had an IPF subgroup may have been a misrepresentation of the actual management costs. For internal consistency with our population criteria, we decided to keep the reference database specific to IPF and excluded diagnostic cost studies from our review.

Our qualitative comparison of HRQoL and cost estimates with population reference statistics has further limitations. The synthesis of evidence from various studies involved the comparison of different EQ-5D versions (3L vs 5L) and conversions of cost estimates to one currency. This required several assumptions about the comparability of the data.

This review excluded relevant conference proceedings (published only as abstracts) before 2015. Records published since 2015 were included. Although the information from an abstract is often limited and the research lacks the scrutiny of an academic journal, we considered it important to include more recent records that report relevant information and that could later be published as full manuscripts. This improves the comprehensiveness of the records presented in this review.

However, the inclusion of abstracts could bias the synthesised data used to estimate the burden of illness. For instance, in the HRQoL studies we included data from the INSIGHTS-IPF registry [80–84] and Fell et al. [12] that at the time were available only as abstracts. In the cost studies we included Hill et al. [88] and Mittmann et al. [94].

In our search for evidence on the burden of IPF, we identified other similar literature reviews. Loveman et al. [26] conducted a systematic review with the objective being the comparison of the clinical effectiveness and cost effectiveness of IPF treatment interventions. Our study was not searching specifically for treatment effects, although there was a lot of overlap in our searches for HRQoL and economic evaluations; we identified the same papers in HRQoL and economic evaluations as Loveman et al. In addition, we have used Loveman et al. to validate our review findings [26] within the overlapping time periods.[4]

Lee et al. [6] reported on the unmet public health need with IPF. Although they cover quality of life and resource utilisation, their analysis on the burden of the disease was focused more around the epidemiology, comorbidities and symptoms of IPF.

The treatment of IPF has changed substantially in recent years, and has evolved a lot since the first paper identified in our search was published (2000). We identified an exponential growth of publications in the last 3–5 years. This trend probably follows the development of new pharmacological interventions such as pirfenidone and nintedanib. For instance, we identified many publications referring to results from three nintedanib clinical trials—TOMORROW, INPULSIS® I and II [25, 110–121].

With the exception of the evidence reported in the cost-effectiveness studies, our review did not capture the full effect of new treatments in IPF. As the pipeline of available treatments expands, new research will be added to the existing data. We recommend a timely update of this review to capture the influx of new studies and any contemporary research. This will be crucial when informing policy decisions in diagnosis, treatment and palliation of patients with IPF.

[4] Some studies included in Loveman et al., not available in the English language, were not selected in our review, given our protocol inclusion criteria.

5 Conclusion

IPF is a chronic, debilitating condition affecting a growing proportion of the population; predominantly male and the elderly. Our review found evidence of an important health burden of the disease in comparison with HRQoL levels of the general population. Furthermore, our review highlighted an excess cost and resource use for healthcare providers. This confirms IPF as a growing threat for public health worldwide with considerable impact on both patients and healthcare providers.

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Author Contributions AD designed and supervised the study and wrote the manuscript with editorial and content input from NS and TM. KV, EW and AD developed the search strategy for the HRQoL and the economic and resource use review. KV, EW, and LC had a substantial contribution to screening of titles, abstracts and full texts with any discrepancies discussed with AD. KV, EW and LC performed the analysis and interpretation of data. All authors approved the final version of the report.

Data availability The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

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Conflict of interest KV, EW, LC and AD are employed by Symmetron Limited, which received funding from Boehringer Ingelheim for this project. AD has in the past received funding from Boehringer Ingelheim for the contribution to original research and similar articles. TM has received consulting fees from Symmetron Limited; industry-academic research funding from GlaxoSmithKline R&D and UCB; and consultancy or speakers fees from AstraZeneca, Bayer, Biogen Idec, Boehringer Ingelheim, Cipla, Dosa, Galapagos, GlaxoSmithKline R&D, ProMetic, Roche (and previously InterMune), Sanofi-Aventis, Takeda and UCB. TM is supported by an NIHR Clinician Scientist Fellowship (NIHR Ref: CS-2013-13-017) and British Lung Foundation Chair in Respiratory Research (C17-3). NS is an employee of Boehringer Ingelheim.

References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824.
2. The National Institute for Health and Care Excellence. Idiopathic pulmonary fibrosis. The diagnosis and management of suspected idiopathic pulmonary fibrosis. 2013.
3. British Thoracic Society. The British Thoracic Society Interstitial Lung Disease Registry Programme. Annual report 2015/16. 2016.
4. Natsuizaka M, Chiba H, Kuronuma K, Otsuka M, Kudo K, Mori M, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med. 2014;190(7):773–9.
5. Vancheri C, Failla M, Crimi N, Raghu G. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. Eur Respir J. 2010;35(3):496–504.
6. Lee AS, Mira-Avendano I, Ryu JH, Daniels CE. The burden of idiopathic pulmonary fibrosis: an unmet public health need. Respir Med. 2014;108(7):955–67.
7. Office for National Statistics. Statistical bulletin: Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2016. 2016. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/latest.
8. Von Plessen C, Grinde O, Gulsvik A. Incidence and prevalence of cryptogenic fibrosing alveolitis in a Norwegian community. Respir Med. 2003;97(4):428–35.
9. Thomeer M, Demedts M, Vandeurzen K. Registration of interstitial lung diseases by 20 centres of respiratory medicine in Flanders. Acta clinica Belgica. 2001;56(3):163–72.
10. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174(7):810–6.
11. Fernandez Perez ER, Daniels CE, Schroeder DR, St Sauver J, Hartman TE, Bartholmai BJ, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. Chest. 2010;137(1):129–37.
12. Fell CD, Hopkins RB, Kolb M, Dion G, Burke N, Goeree R. Prevalence and incidence of idiopathic pulmonary fibrosis in Canada. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS, 2015, p. 191.
13. Ohno S, Nakaya T, Bando M, Sugiyama Y. Idiopathic pulmonary fibrosis–results from a Japanese nationwide epidemiological survey using individual clinical records. Respirology. 2008;13(6):926–8.
14. Navaratnam V, Fleming KM, West J, Smith CJ, Jenkins RG, Fogarty A, et al. The rising incidence of idiopathic pulmonary fibrosis in the U.K. Thorax. 2011;66(6):462–7.
15. Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. Eur Respir Rev. 2012;21(126):355–61.
16. European Medicines Agency. CHMP assessment report. EMA/76777/2015. 2015.
17. European Medicines Agency. CHMP assessment report. EMA/CHMP/115147/2011. 2011.
18. US Food and Drug Administration. FDA approves Esbriet to treat idiopathic pulmonary fibrosis. 2014. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM418991_F.
19. ClinicalTrials.gov. A Phase 2, Randomized Dose-ranging Study to Evaluate the Efficacy of Tralokinumab in Adults With

Idiopathic Pulmonary Fibrosis [NCT01629667] 2017. https://www.clinicaltrials.gov/ct2/show/NCT01629667?term=Tralokinumab&rank=2.
20. ClinicalTrials.gov. Study to assess the efficacy and safety of simtuzumab (GS-6624) in adults with idiopathic pulmonary fibrosis (IPF) (RAINIER) [NCT01769196]. 2013.
21. ClinicalTrials.gov. Efficacy and safety of SAR156597 in the treatment of idiopathic pulmonary fibrosis (ESTAIR) [NCT02345070] 2015. . https://clinicaltrials.gov/ct2/show/NCT02345070?term=NCT02345070&rank=1.
22. ClinicalTrials.gov. A study of lebrikizumab in participants with idiopathic pulmonary fibrosis [NCT01872689] 2013. https://clinicaltrials.gov/ct2/show/NCT01872689?term=NCT01872689&rank=1.
23. ClinicalTrials.gov. Evaluate the safety and efficacy of FG-3019 in patients with idiopathic pulmonary fibrosis [NCT01890265] 2013. https://clinicaltrials.gov/ct2/show/NCT01890265?term=NCT01890265&rank=1.
24. ClinicalTrials.gov. A trial to evaluate the efficacy of PRM-151 in subjects with idiopathic pulmonary fibrosis (IPF) [NCT02550873] 2016. https://clinicaltrials.gov/ct2/show/NCT02550873?term=NCT02550873&rank=1.
25. Rinciog C, Watkins M, Chang S, Maher T, LeReun C, Esser D, et al. Nintedanib cost-effectiveness in idiopathic pulmonary fibrosis in the UK. Value Health. 2016;19(7):A553.
26. Loveman E, Copley VR, Colquitt J, Scott DA, Clegg A, Jones J, et al. The clinical effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: a systematic review and economic evaluation. [Review]. Health Technol Assess. 2015;19(20):1–336.
27. Bors M, Tomic R, Perlman DM, Kim HJ, Whelan TP. Cognitive function in idiopathic pulmonary fibrosis. Chronic Respir Dis. 2015;12(4):365–72.
28. Gaunaurd IA, Gomez-Marin OW, Ramos CF, Sol CM, Cohen MI, Cahalin LP, et al. Physical activity and quality of life improvements of patients with idiopathic pulmonary fibrosis completing a pulmonary rehabilitation program. Respir Care. 2014;59(12):1872–9.
29. Natalini JG, Swigris JJ, Morisset J, Elicker BM, Jones KD, Fischer A, et al. Understanding the determinants of health-related quality of life in rheumatoid arthritis-associated interstitial lung disease. Respir Med. 2017;127:1–6.
30. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, et al. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. Respir Med. 2014;108(1):203–10.
31. Sharma N, Bhatt S, Luckhardt T, De Aandrade J. Short term outcomes of pulmonary rehabilitation in idiopathic pulmonary fibrosis. Chest Conference 2014.
32. Yount SE, Beaumont JL, Chen SY, Kaiser K, Wortman K, Van Brunt DL, et al. Health-related quality of life in patients with idiopathic pulmonary fibrosis. Lung. 2016;194(2):227–34.
33. Han M, Swigris J, Liu L, Bartholmai B, Murray S, Giardino N, et al. Gender influences health-related quality of life in IPF. Respir Med. 2010;104(5):724–30.
34. Lubin M, Chen H, Elicker B, Jones K, Collard H, Lee J. A comparison of health-related quality of life in idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. Chest. 2014;145(6):1333–8.
35. Raghu G, Brown KK, Costabel U, Cottin V, du Bois RM, Lasky JA, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. Am J Respir Crit Care Med. 2008;178(9):948–55.
36. Swigris J, Fairclough D, Morrison M, Make B, Kozora E, Brown K, et al. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. Respir Care. 2011;56(6):783–9.
37. Swigris J, Wilson S, Green K, Sprunger D, Brown K, Wamboldt F. Development of the ATAQ-IPF: a tool to assess quality of life in IPF. Health Qual Life Outcomes. 2010;8:77.
38. Horton MR, Santopietro V, Mathew L, Horton KM, Polito AJ, Liu MC, et al. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: a randomized trial. Ann Intern Med. 2012;157(6):398–406.
39. Martinez FJ, de Andrade JA, Anstrom KJ, King TE Jr, Raghu G, Idiopathic Pulmonary Fibrosis Clinical Research Network. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2093–101.
40. Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and *N*-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366(21):1968–77.
41. Collard HR, Chen SY, Yeh WS, Li Q, Lee YC, Wang A, et al. Health care utilization and costs of idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older. Ann Am Thorac Soc. 2015;12(7):981–7.
42. Collard HR, Ward AJ, Lanes S, Cortney Hayflinger D, Rosenberg DM, Hunsche E. Burden of illness in idiopathic pulmonary fibrosis. J Med Econ. 2012;15(5):829–35.
43. Mooney JJ, Raimundo K, Chang E, Broder MS. Hospital cost and length of stay in idiopathic pulmonary fibrosis. J Med Econ. 2017;20(5):518–24.
44. Raimundo K, Chang E, Broder MS, Alexander K, Zazzali J, Swigris JJ. Clinical and economic burden of idiopathic pulmonary fibrosis: a retrospective cohort study. BMC Pulm Med. 2016;16(2):05.
45. Sharif R, Zouk A, Kulkarni T, Acosta P, Duncan S, Luckhardt T, et al. Cost of hospitalization among patients with idiopathic pulmonary fibrosis: patterns and predictors. Chest Conference: CHEST, October 2016, United States 2016.
46. Yu Y, Goehring E, Nguyen-Khoa BA, Holmes J, Jones J, Evans A, et al. Comorbidity burden and healthcare resource use in patients with idiopathic pulmonary fibrosis (IPF) in the United States (US) military health system. Chest Conference: CHEST October 2014, Austin, TX United States 2014.
47. Yu YF, Macaulay DS, Reichmann WM, Wu EQ, Nathan SD. Association of early suspected acute exacerbations of idiopathic pulmonary fibrosis with subsequent clinical outcomes and healthcare resource utilization. Respir Med. 2015;109(12):1582–8.
48. Yu YF, Wu N, Chuang CC, Wang R, Pan X, Benjamin NN, et al. Patterns and economic burden of hospitalizations and exacerbations among patients diagnosed with idiopathic pulmonary fibrosis. J Manag Care Spec Pharm. 2016;22(4):414–23.
49. The World Bank. World Bank Country and Lending Groups. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.
50. Morsi TS, Ghobashy S, Younis G. Quality of life and psychological disorders in Egyptian patients with chronic lung diseases: clinico-physiological correlation. Egypt J Chest Dis Tuberc. 2014;63(3):731–43.
51. Rifaat N, Anwar E, Ali YM, Ellabban A, Hasan A. Value of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. European Respiratory Journal Conference: European Respiratory Society Annual Congress. 2014, p. 44.
52. Mishra A, Bhattacharya P, Paul S, Paul R, Swarnakar S. An alternative therapy for idiopathic pulmonary fibrosis by doxycycline through matrix metalloproteinase inhibition. Lung India. 2011;28(3):174–9.
53. Furukawa T, Taniguchi H, Ando M, Kondoh Y, Kataoka K, Nishiyama O, et al. The St. George's Respiratory Questionnaire as a prognostic factor in IPF. Respir Res. 2017;18(1):18.
54. Matsuda T, Taniguchi H, Ando M, Kondoh Y, Kimura T, Kataoka K, et al. COPD Assessment Test for measurement of

health status in patients with idiopathic pulmonary fibrosis: a cross-sectional study. Respirology. 2017;22(4):721–7.
55. Tomioka H, Mamesaya N, Yamashita S, Kida Y, Kaneko M, Sakai H. Combined pulmonary fibrosis and emphysema: Effect of pulmonary rehabilitation in comparison with chronic obstructive pulmonary disease. BMJ Open Respir Res. 2016;3(1):e000099.
56. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2008;13(3):394–9.
57. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Kataoka K, Nishimura K, et al. Health-related quality of life does not predict mortality in idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2012;29(2):113–8.
58. Kozu R, Senjyu H, Jenkins S, Mukae H, Sakamoto N, Kohno S. Differences in response to pulmonary rehabilitation in idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. Respiration. 2011;81(3):196–205.
59. Kozu R, Jenkins S, Senjyu H. Effect of disability level on response to pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2011;16(8):1196–202.
60. Tomioka H, Imanaka K, Hashimoto K, Iwasaki H. Health-related quality of life in patients with idiopathic pulmonary fibrosis-cross-sectional and longitudinal study. Intern Med. 2007;46(18):1533–42.
61. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F, et al. Health-related quality of life in patients with idiopathic pulmonary fibrosis. What is the main contributing factor? Respir Med. 2005;99(4):408–14.
62. Peng S, Li Z, Kang J, Hou X. Cross-sectional and longitudinal construct validity of the Saint George's Respiratory Questionnaire in patients with IPF. Respirology. 2008;13(6):871–9.
63. Kim SW, Myong JP, Yoon HK, Koo JW, Kwon SS, Kim YH. Health care burden and medical resource utilisation of idiopathic pulmonary fibrosis in Korea. Int J Tuberc Lung Dis. 2017;21(2):230–5.
64. Jarosch I, Schneeberger T, Gloeckl R, Kreuter M, Neurohr C, Prasse A, et al. Effects of a 3-week pulmonary rehabilitation program in patients with idiopathic pulmonary fibrosis-a randomized, controlled trial. Conference: European Respiratory Society Annual Congress: European Respiratory Journal, 2016.
65. Kramer M, Vainshelboim B, Oliveira J, Yohoshua L, Wais I, Rusanov V, et al. Pulmonary rehabilitation improves exercise capacity and function in patients with idiopathic pulmonary fibrosis. American Thoracic Society International Conference, ATS American Journal of Respiratory and Critical Care Medicine, 2014.
66. Nolan CM, Kon SSC, Canavan JL, Jones SE, Maddocks M, Cullinan P, et al. Preferential lower limb muscle weakness in idiopathic pulmonary fibrosis: Effects on exercise capacity. European Respiratory Journal Conference: European Respiratory Society Annual Congress, 2014, p. 44.
67. Zisman D, Schwarz M, Anstrom K, Collard H, Flaherty K, Hunninghake G. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med. 2010;363(7):620–8.
68. Antoniou K, Nicholson A, Dimadi M, Malagari K, Latsi P, Rapti A, et al. Long-term clinical effects of interferon gamma-1b and colchicine in idiopathic pulmonary fibrosis. Eur Respir J. 2006;28(3):496–504.
69. Jastrzebski D, Kozielski J, Banas A, Cebula T, Gumola A, Ziora D, et al. Quality of life during one-year observation of patients with idiopathic pulmonary fibrosis awaiting lung transplantation. J Physiol Pharmacol. 2005;56(Suppl. 4):99–105.
70. Yorke J, Jones PW, Swigris JJ. Development and validity testing of an IPF-specific version of the St George's Respiratory Questionnaire. Thorax. 2010;65(10):921–6.
71. Gaunaurd IA, Cardenas DD, Cahalin LP, Cohen MI, Ramos CF, Jackson RM, et al. Health-related quality of life of IPF patients in a pulmonary rehabilitation program. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS, 2014, p. 189.
72. Gomez O, Gaunaurd IA, Cohen M, Cardenas D, Cahalin L, Ramos C. Health-related quality of life in IPF patients on a pulmonary rehabilitation program. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS, 2014, p. 189.
73. Ferrara G, Carlson L, Palm A, Einarsson J, Olivesten C, Skold M. Idiopathic pulmonary fibrosis in Sweden: report from the first year of activity of the Swedish IPF-Registry. Eur Clin Respir J. 2016;3:310–90.
74. Kreuter M, Wirtz H, Prasse A, Pittrow D, Koschel D, Klotsche J, et al. Symptoms and quality of life in relation to lung function and comorbidities in patients with idiopathic pulmonary fibrosis: INSIGHTS-IPF registry. European Respiratory Journal Conference: European Respiratory Society Annual Congress, 2016, p. 48.
75. King TE Jr, Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;184(1):92–9.
76. Freemantle N, Wilson A, Fisher M. Mapping the St george's respiratory questionnaire to the Euroqol 5 dimensions: a study in patients with idiopathic pulmonary fibrosis. Value Health. 2015;18(7):A503.
77. Swigris JJ, Brown KK, Behr J, du Bois RM, King TE, Raghu G, et al. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. Respir Med. 2010;104(2):296–304.
78. Szende A, Janssen B, Cabases J. Population norms for the EQ-5D. Self-reported population health: an international perspective based on EQ-5D. Dordrecht: Springer; 2014.
79. Fryback DG, Dunham NC, Palta M, Hanmer J, Buechner J, Cherepanov D, et al. US norms for six generic health-related quality-of-life indexes from the National Health Measurement study. Med Care. 2007;45(12):1162–70.
80. Behr J, Kreuter M, Hoeper M, Klotsche J, Wirtz H, Koschel D, et al. Late-breaking abstract: Current management of patients with idiopathic pulmonary fibrosis in clinical practice: INSIGHTS-IPF registry. European Respiratory Journal Conference: European Respiratory Society Annual Congress, 2014, p. 44.
81. Behr J, Kreuter M, Wirtz H, Hoeper M, Klotsche J, Koschel D, et al. Insights on the management of patients with idiopathic pulmonary fibrosis in clinical practice: Insights-IPF. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS, 2014, p. 189.
82. Behr J, Wirtz H, Pittrow D, Klotsche J, Koschel D, Andreas S, et al. Clinical course of patients with idiopathic pulmonary fibrosis under real life conditions: Outcomes data of the insights-IPF register. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS, 2015, p. 191.
83. Kreuter M, Birring SS, Wijsenbeek M, Wapenaar M, Oltmanns U, Costabel U, et al. German validation of the "King's Brief Interstitial Lung Disease (K-Bild) Health Status Questionnaire". [German] Deutschsprachige Validierung des "King's Brief Interstitial Lung Disease (K-BILD)" Lebensqualitatsfragebogens fur interstitielle Lungenerkrankungen. Pneumologie. 2016;70(11):742–6.

84. Pittrow D, Klotsche J, Kreuter M, Hoeper MM, Wirtz H, Koschel D, et al. Symptom burden and health related quality of life in patients with idiopathic pulmonary fibrosis in clinical practice: insights-IPF registry. Value Health. 2014;17(7):A600.
85. Yazdani A, Singer LG, Strand V, Gelber AC, Williams L, Mittoo S. Survival and quality of life in rheumatoid arthritis-associated interstitial lung disease after lung transplantation. J Heart Lung Transplant. 2014;33(5):514–20.
86. King J, Behr J, Brown K, Du Bois R, Lancaster L, De Andrade J, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2008;177(1):75–81.
87. Goode CC, Mulgirigama A, Mathieson N. Idiopathic pulmonary fibrosis exacerbations: what is the cost of the diagnosis? CONFERENCE ABSTRACT: American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS 2014. San Diego: Conference Publication; 2014.
88. Hill C, Nasr R, Fisher MI, Maher T, Spiteri M, Allen M, et al. Estimated cost and payment by results (PBR) tariff reimbursement for idiopathic pulmonary fibrosis services across 14 specialist providers in England. CONFERENCE ABSTRACT: Thorax. Conference: British Thoracic Society Winter Meeting 2014. London: Conference Publication; 2014.
89. Nasr R, Kausar I, Chaudhuri N. Cost burden of n-acetylcysteine (NAC) in adult patients with idiopathic pulmonary fibrosis. CONFERENCE ABSTRACT: Thorax. Conference: British Thoracic Society Winter Meeting 2014. London: Conference Publication; 2014.
90. Diamantopoulos A, Schoof N, Esser D, LeReun C. Resource use in idiopathic pulmonary fibrosis: Influence of disease progression and exacerbations. CONFERENCE ABSTRACT: Value in Health. Conference: ISPOR 19th Annual European Congress, Austria, 2016.
91. Morell F, Esser D, Lim J, Stowasser S, Villacampa A, Nieves D, et al. Treatment patterns, resource use and costs of idiopathic pulmonary fibrosis in Spain—results of a Delphi panel. BMC Pulm Med. 2016;16(7):12.
92. Parfrey H, Leonard C, Gibbons MA, Armstrong E, Harris E, Frank R, et al. Healthcare utilisation by patients with idiopathic pulmonary fibrosis; observations from the UK pirfenidone named patient programme. Thorax. 2013;68:A164–5.
93. Wu N, Yu YF, Chuang CC, Wang R, Benjamin NN, Coultas DB. Healthcare resource utilization among patients diagnosed with idiopathic pulmonary fibrosis in the United States. J Med Econ. 2015;18(4):249–57.
94. Mittmann N, Hassan S, Seung SJ, Saherawala H, Hoffstein V, Bradley-Kennedy C. Examining health system and resource utilization and medical management of patients idiopathic pulmonary fibrosis in Ontario: a preliminary analysis. CONFERENCE ABSTRACT: Value in Health. Conference: ISPOR 18th Annual European Congress. Milan: Conference Publication; 2015.
95. Pedraza-Serrano F, De Andres AL, Jimenez-Garcia R, Jimenez-Trujillo I, Hernandez-Barrera V, Sanchez-Munoz G, et al. Emerging drugs and therapeutics for systemic sclerosis. EMBASE. 2016;21(4):421–30.
96. The Organisation for Economic Co-operation and Development. Health spending. https://data.oecd.org/healthres/health-spending.htm.
97. Pedraza-Serrano F, De Andres AL, Jimenez-Garcia R, Jimenez-Trujillo I, Hernandez-Barrera V, Sanchez-Munoz G, et al. Retrospective observational study of trends in hospital admissions for idiopathic pulmonary fibrosis in Spain (2004–2013) using administrative data. BMJ Open. 2017;7(2):e013156.
98. Wilson EC, Shulgina L, Cahn AP, Chilvers ER, Parfrey H, Clark AB, et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: an economic evaluation alongside a randomised controlled trial. Pharmacoeconomics. 2014;32(1):87–99.
99. Benard S, Schmidt A, Catella L, Porte F, Setton M, Fernandez-Montoya C, et al. Nintedanib cost-utility in idiopathic pulmonary fibrosis in France. Value Health. 2016;19(7):A556.
100. Tritaki G, Souliotis K, Bouros D, Papageorgiou I, Diamantopoulos A, Rinciog C, et al. Pharmacoeconomic assessment of nintedanib for the treatment of idiopa thic pulmonary fibrosis in the Greek healthcare system. CONFERENCE ABSTRACT: Value in Health. Conference: ISPOR 19th Annual European Congress, Austria, 2016.
101. Capano F, Filieri A, Lerda C, Bandelli GP, Buscaino A, Ielo D. Pirfenidone for treatment of idiopathic pulmonary fibrosis: cost effectiveness evaluation. Int J Clin Pharmacy. 2016;38(6):566.
102. Ravasio R, Ferrario M, Pata M, Thuresson P. Cost effectiveness analysis of pirfenidone for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF) compared to best supportive care and nintedanib from the Italian NHS perspective. Value Health. 2016;19(7):A556.
103. Soulard S, Crespo C. Cost-utility of nintedanib vs. pirfenidone in the treatment of idiopathic pulmonary fibrosis in Spain. Value Health. 2016;19(7):A555.
104. Pozo L, Paladio-Hernandez J. Cost-effective evaluation of pirfenidone for treating idiopathic pulmonary fibrosis in Mexico. Value Health. 2015;18(7):A840–1.
105. Hagaman JT, Kinder BW, Eckman MH. Thiopurine *S*-methyltransferase [corrected] testing in idiopathic pulmonary fibrosis: a pharmacogenetic cost-effectiveness analysis.[Erratum appears in Lung. 2011 Jun; 189(3):259]. Lung. 2010;188(2):125–32.
106. Pittrow D, Klotsche J, Kreuter M, Hoeper MM, Wirtz H, Koschel D, et al. Symptom burden and health related quality of life in patients with idiopathic pulmonary fibrosis in clinical practice: insights-Ipf registry. Value Health. 2014;17(7):A600.
107. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health. 2011;14(4):539–45.
108. Manuel DG, Schultz SE, Kopec JA. Measuring the health burden of chronic disease and injury using health adjusted life expectancy and the Health Utilities Index. J Epidemiol Community Health. 2002;56(11):843–50.
109. Sharp C, McCabe M, Adamali H, Medford AR. Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease—a systematic review and cost analysis. QJM. 2017;110(4):207–14.
110. Azuma A, Taniguchi H, Inoue Y, Kondoh Y, Ogura T, Homma S, et al. Nintedanib in Japanese patients with idiopathic pulmonary fibrosis: a subgroup analysis of the INPULSIS randomized trials. Respirology. 2017;22(4):750–7.
111. Costabel U, Inoue Y, Richeldi L, Collard HR, Tschoepe I, Stowasser S, et al. Efficacy of nintedanib in idiopathic pulmonary fibrosis across prespecified subgroups in INPULSIS. Am J Respir Crit Care Med. 2016;193(2):178–85.
112. Gohn N, Richeldi L, Cottin V, Selman M, Kimura T, Stowasser S, et al. Pooled analysis of data from the tomorrow and INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis. Respirology. 2016;21:148.
113. Huggins J, Kaye M, Bailes Z, Esser D, Conoscenti C, Flaherty K. Efficacy and safety of nintedanib in US and Non US patients with idiopathic pulmonary fibrosis (IPF) in the INPULSIS trials. Chest Conference: CHEST. 2015;148(4 meeting abstract).
114. Kolb M, Kimura T, Stowasser S, Hallmann C, du Bois R. Effect of baseline FVC on decline in lung function with nintedanib in

patients with IPF: results from the INPULSIS® trials. Am Thorac Soc. 2015.
115. Raghu G, Wells A, Nicholson AG, Richeldi L, Flaherty KR, Le Maulf F, et al. Consistent effect of nintedanib on decline in FVC in patients across subgroups based on HRCT diagnostic criteria: results from the INPULSIS trials in IPF. Thorax. 2015;70:A60–1.
116. Richeldi L, Brown KK, Cottin V, Selman M, Kimura T, Stowasser S. Pooled analysis of data from the tomorrow and INPULSIS trials of nintedanib in IPF. Thorax. 2015;70:A78.
117. Richeldi L, Costabel U, Selman M, Kim D, Hansell D, Nicholson A, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011;365(12):1079–87.
118. Richeldi L, Cottin V, du Bois RM, Selman M, Kimura T, Bailes Z, et al. Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS trials. Respir Med. 2016;6(113):74–9.
119. Richeldi L, Du Bois R, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis: results of two 52-week, phase III, randomized, placebo-controlled trials (INPULSIS™). American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS, 2014, p. 189.
120. Ryerson C, Kolb M, Richeldi L, Lee J, Kimura T, Stowasser S, et al. Effect of baseline gap index stage on decline in lung function with nintedanib in patients with idiopathic pulmonary fibrosis (IPF). QJM. 2016;109:S52.
121. Taniguchi H, Xu Z, Azuma A, Inoue Y, Li H, Fujimoto T, et al. Subgroup analysis of Asian patients in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis. Respirology. 2016;21(8):1425–30.
122. Alhamad EH. Pirfenidone treatment in idiopathic pulmonary fibrosis: a Saudi experience. Ann Thorac Med. 2015;10(1):38–43.
123. Baddini Martinez J, Martinez T, Lovetro Galhardo F, De Castro Pereira C. Dyspnea scales as a measure of health-related quality of life in patients with idiopathic pulmonary fibrosis. Med Sci Monit. 2002;8(6):CR405–10.
124. Bahmer T, Kirsten AM, Waschki B, Rabe KF, Magnussen H, Kirsten D, et al. Clinical correlates of reduced physical activity in idiopathic pulmonary fibrosis. Respiration. 2016;91(6):497–502.
125. Crooks MG, Dudziak J, Morice AH, Hart SP. Cough in idiopathic pulmonary fibrosis: a sign of "silent" gastroesophageal reflux. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS, 2014, p. 189.
126. De Vries J, Seebregts A, Drent M. Assessing health status and quality of life in idiopathic pulmonary fibrosis: which measure should be used? Respir Med. 2000;94(3):273–8.
127. Dowman LM, McDonald CF, Hill CJ, Lee A, Barker K, Boote C, et al. Effect of disease aetiology on response to exercise training in patients with interstitial lung disease. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS, 2015, p. 191.
128. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, et al. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. Thorax. 2017;72(7):610–9.
129. Elfferich M, De Fries J, Drent M. Type D or 'distressed' personality in sarcoidosis and idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2011;28(1):65–71.
130. Glaspole IN, Chapman SA, Cooper WA, Ellis SJ, Goh NS, Hopkins PM, et al. Health-related quality of life in idiopathic pulmonary fibrosis: data from the Australian IPF registry. Respirology. 2017;22(5):950–6.
131. Jo HE, Glaspole I, Grainge C, Goh N, Hopkins PM, Moodley Y, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian idiopathic pulmonary fibrosis registry. Eur Respir J. 2017;49(2):pii.
132. Jones RM, Hilldrup S, Hope-Gill BD, Eccles R, Harrison NK. Mechanical induction of cough in idiopathic pulmonary fibrosis. Cough. 2011;7:2.
133. Key AL, Holt K, Hamilton A, Smith JA, Earis JE. Objective cough frequency in idiopathic pulmonary fibrosis. Cough. 2010;6:4.
134. Raghu G, King TE, Behr J, Brown KK, Du Bois RM, Leconte I, Roux S, Swigris J. Quality of life and dyspnoea in patients treated with bosentan for idiopathic pulmonary fibrosis (BUILD-1). Eur Respir J. 2010;35(1):118–23.
135. Kotecha J, Atkins C, Wilson A. Patient confidence and quality of life in idiopathic pulmonary fibrosis and sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2016;33(4):341–8.
136. Kozu R, Jenkins S, Senjyu H. Evaluation of activity limitation in patients with idiopathic pulmonary fibrosis grouped according to medical research council dyspnea grade. Arch Phys Med Rehabil. 2014;95(5):950–5.
137. Lutogniewska W, Jastrzebski D, Wyrwol J, Ksiazek B, Ochman M, Kowalski K, et al. Dyspnea and quality of life in patients referred for lung transplantation. Eur J Med Res. 2010;15(Suppl 2):76–8.
138. Martinez T, Pereira C, Dos Santos M, Ciconelli R, Guimaraes S, Martinez J. Evaluation of the short-form 36-item questionnaire to measure health- related quality of life in patients with idiopathic pulmonary fibrosis. Chest. 2000;117(6):1627–32.
139. Mermigkis C, Bouloukaki I, Antoniou K, Mermigkis D, Psathakis K, Giannarakis I, et al. CPAP therapy in patients with idiopathic pulmonary fibrosis and obstructive sleep apnea: does it offer a better quality of life and sleep? Sleep Breath. 2013;17(4):1137–43.
140. Mermigkis C, Bouloukaki I, Antoniou K, Papadogiannis G, Giannarakis I, Varouchakis G, et al. Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis. Sleep Breath. 2014;19(1):385–91.
141. Nathan SD, Du Bois RM, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. Respir Med. 2015;109(7):914–22.
142. Ntolios P, Karampitsakos T, Karailidou M, Xanthoudaki M, Nena E, Kotakidou D, et al. Sleep quality among patients with idiopathic pulmonary fibrosis. European Respiratory Journal Conference: European Respiratory Society Annual Congress 2015.
143. Ozalevli S, Karaali H, Ilgin D, Ucan E. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Multidiscip Respir Med. 2010;5(1):31–7.
144. Raghu G, Martinez FJ, Brown KK, Costabel U, Cottin V, Wells AU, et al. CC-chemokine ligand 2 inhibition in idiopathic pulmonary fibrosis: a phase 2 trial of carlumab. Eur Respir J. 2015;46(6):1740–50.
145. Tzanakis N, Samiou M, Lambiri I, Antoniou K, Siafakas N, Bouros D. Evaluation of health-related quality-of-life and dyspnea scales in patients with idiopathic pulmonary fibrosis. Correlation with pulmonary function tests. Eur J Intern Med. 2005;16(2):105–12.
146. Tzouvelekis A, Paspaliaris V, Koliakos G, Ntolios P, Bouros E, Oikonomou A, et al. A prospective, non-randomized, no

placebo-controlled, phase Ib clinical trial to study the safety of the adipose derived stromal cells-stromal vascular fraction in idiopathic pulmonary fibrosis. J Transl Med. 2013;11:171.
147. Vainshelboim B, Oliveira J, Fox B, Kramer M. Effect of exercise pulmonary rehabilitation on long-term outcomes in idiopathic pulmonary fibrosis. European Respiratory Journal Conference: European Respiratory Society Annual Congress 2014.
148. Vainshelboim B, Oliveira J, Fox BD, Soreck Y, Fruchter O, Kramer MR. Long-term effects of a 12-week exercise training program on clinical outcomes in idiopathic pulmonary fibrosis. Lung. 2015;193(3):345–54.
149. Verma G, Marras T, Chowdhury N, Singer L. Health-related quality of life and 6 min walk distance in patients with idiopathic pulmonary fibrosis. Can Respir J. 2011;18(5):283–7.
150. Wuyts W, Bondue B, Dahlqvist C, Slabbynk H, Schlesser M, Gusbin N, et al. PROOF-registry: A prospective observational registry to describe the disease course and outcomes of IPF patients in a real-world clinical setting-An interim report. European Respiratory Journal Conference: European Respiratory Society Annual Congress 2015.
151. Wuyts WA, Peccatori FA, Russell AM. Patient-centred management in idiopathic pulmonary fibrosis: similar themes in three communication models. [Review]. Eur Respir Rev. 2014;23(132):231–8.
152. Zimmermann C, Carvalho C, Silveira K, Yamaguti W, Moderno E, Salge J, et al. Comparison of two questionnaires which measure the health-related quality of life of idiopathic pulmonary fibrosis patients. Braz J Med Biol Res. 2007;40(2):179–87.
153. Chen SY, Collard HR, Yeh WS, Li Q, Lee YC, Wang A, et al. An analysis of us medicare beneficiaries: burden of direct medical costs in patients with idiopathic pulmonary fibrosis. Value Health. 2014;17(7):A592.
154. Cottin V, Schmidt A, Catella L, Porte F, Fernandez-Montoya C, Le Lay K, et al. Idiopathic pulmonary fibrosis: hospital disease management and associated costs. Value Health. 2015;18(7):A665.
155. Cottin V, Schmidt A, Catella L, Porte F, Fernandez-Montoya C, Le Lay K, et al. Burden of idiopathic pulmonary fibrosis progression: a 5-year longitudinal follow-up study. PLoS ONE. 2017;12(1):e0166462.
156. Kim CH, Kim JY, Hwang YI, Lee CY, Choi JH, Park YB, et al. Interferon-gamma enzyme-linked immunospot assay in patients with tuberculosis and healthy adults. Tuberc Respir Dis. 2014;76(1):23–9.
157. Mooney J, Raimundo K, Chang E, Broder M. Mortality, costs and length of stay in patients with idiopathic pulmonary fibrosis (IPF). CONFERENCE ABSTRACT: QJM. Conference: 19th International Colloquium on Lung and Airway Fibrosis. Ireland 2016.
158. Navaratnam V, Fogarty AW, Glendening R, McKeever T, Hubbard RB. The increasing secondary care burden of idiopathic pulmonary fibrosis: hospital admission trends in England from 1998 to 2010. Chest. 2013;143(4):1078–84.
159. Raimundo K, Chang E, Broder M, Carrigan G, Zazzali J, Swigris JJ. Clinical and economic burden of idiopathic pulmonary fibrosis. American Thoracic Society International Conference, ATS 2015; Denver, United States: American Journal of Respiratory and Critical Care Medicine 2015.
160. Loveman E, Copley VR, Colquitt JL, Scott DA, Clegg AJ, Jones J, et al. The effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: systematic review, network meta-analysis and health economic evaluation. BMC Pharmacol Toxicol. 2014;15:63.