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Early View

Original article

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Pharmacological and non-pharmacological interventions to improve symptom control, functional exercise capacity and quality of life in interstitial lung disease: an evidence synthesis

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Abstract
We assessed efficacy and effectiveness of pharmacological and non-pharmacological interventions in improving symptom control, functional exercise capacity and quality of life (Qol) in people living with fibrotic interstitial lung disease (ILD).

We summarised evidence from three previous reviews (to June 2014) and conducted an updated search of nine databases and grey literature (2011-19) (registration: CRD42017065933) for prospective studies of interventions aimed to alleviate symptoms, improve Qol or functional exercise capacity in fibrotic ILD. Data were synthesised through narrative synthesis or meta-analysed as appropriate.

Forty-seven studies with 2,527 participants were included. From 22 pharmacological studies of eleven different interventions (n=1,683) the most tested interventions were bosentan and sildenafil. From 25 non-pharmacological studies, the most tested intervention was for pulmonary rehabilitation / exercise training (PR) (22 studies, n=748). An improvement in 6-minute walk distance (6MWD) immediately following PR (6 studies; n=200, MD [95%CI] 39.9 m [18.2 to 61.5]) but not longer-term (3 or 6 months, 4 studies; n=147, MD 5.3 m [-12.9 to 23.4]. Multiple, varied outcome measures were used, e.g. 37 studies assessing dyspnoea used 10 different scales with lack of reporting of rate of deterioration in outcomes. Evidence gap mapping highlighted the most and least researched symptoms were dyspnoea and cough respectively.

This evidence synthesis highlights overwhelmingly that the most researched symptom is dyspnoea and the strongest evidence base is for short-term PR. The least researched symptom was cough. Research going forward must focus on prioritising and standardising meaningful outcomes and focusing interventions on neglected symptoms.

Social media take home message: Cough is a neglected symptom in ILD. Future research must prioritise and standardise meaningful outcomes and focus interventions on neglected symptoms whilst ensuring dyspnoea is prioritised as a primary end point for future studies.

Introduction

Rationale

Patients with Interstitial Lung Disease (ILD) can live for many years, with some ILDs responsive to treatment. However, fibrotic ILDs (such as idiopathic pulmonary fibrosis (IPF)) have a shorter disease trajectory which can be rapidly advancing.[1] The resulting physical and psychological burden with impact on quality of life (Qol), can be substantial for both patients and carers.[2] A recent pivotal ILD position statement stressed the need to deliver early and effective palliative care and the importance of "*living as well as possible"* as disease advances.[3] Essential to achieving this is to improve symptom management and Qol as well as improving functional exercise capacity. Previous systematic reviews have summarised interventions to improve symptoms and Qol in ILD, [4, 5] [6] (see online Suppl1 for further details). As the importance of improving the symptoms, functional exercise capacity and Qol of these patients has become increasingly recognised [7, 8], there has been a surge in intervention studies. There is therefore a need to synthesise previous research with more recently published studies and highlight areas in which we may move research forward in a meaningful way.

Objectives

We aim to synthesise relevant studies from three previous systematic reviews with more recently published studies and highlight gaps in research through an evidence gap map.

Methods

Protocol and registration

The systematic review was carried out in line with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines and the protocol is registered on the PROSPERO database (CRD42017065933). The protocol stated that participants with a confirmed diagnosis of ILD would be included. However, after reflection within the Project Advisory Team, to limit heterogeneity, it was decided to focus on fibrotic ILDs only as they all shared the commonality of shorter disease trajectory, severity of symptoms and poor functional exercise capacity.

Eligibility criteria

We included studies recruiting participants with a confirmed clinical or pathological/radiological diagnosis of a fibrotic ILD (including, but not restricted to IPF and non-specific interstitial pneumonia). We excluded studies in people with connective tissue ILDs or obstructive sleep apnoea and those for which the breakdown of ILD diagnoses was not available. Eligible interventions were any pharmacological or non-pharmacological intervention aimed at managing symptoms or improving Qol (such as oxygen therapy, opioids, corticosteroids and non-invasive ventilation) or functional exercise capacity (as measured by 6MWD). Radical disease modifying interventions, that were evaluated in studies primarily focused on improving survival and lung function, were deemed out of scope. We accepted any comparators/controls. Eligible outcomes were all symptom control outcomes (such as breathlessness, cough and fatigue), Qol outcomes and 6MWD. Prospective efficacy and effectiveness studies of any design were eligible including observational (e.g. cohort studies) and interventional prospective studies (e.g. randomised controlled studies, controlled clinical trials, before and after studies).

Information sources:

Two authors (AO & SB) independently screened studies that were included in the previous reviews [4, 5] [6] for inclusion. In addition, nine electronic databases were searched for journal articles, meeting abstracts, ongoing studies and reviews from 2011 to January 2019 with no language restrictions: Ovid MEDLINE, Ovid EMBASE, Web of Science Core Collection, Cochrane library, CRD databases, NIH ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), UK Clinical Trials Gateway and PROSPERO.

Reference lists of included studies were screened and experts in the field contacted to identify additional studies. Searches of grey literature, conference proceedings and research in progress databases were also conducted.

Search

A combination of MESH headings and keywords were used. For example in Medline, the following terms were combined: Lung Diseases, Interstitial/dt, pc, rh, su [Drug Therapy,

Prevention & Control, Rehabilitation, Surgery] OR Idiopathic Pulmonary Fibrosis/dt, pc, rh, su [Drug Therapy, Prevention & Control, Rehabilitation, Surgery] OR Idiopathic Interstitial Pneumonias/dt, pc, th [Drug Therapy, Prevention & Control, Therapy] OR interstitial lung disease*.tw OR idiopathic pulmonary fibrosis.tw OR non-specific interstitial pneumonia*.tw OR idiopathic interstitial pneumonia*.tw OR cryptogenic organi* pneumonia*.tw NOT (comment or letter or editorial).pt. The searches were then limited to 2011 to current year. The full search strategy can be found in online Suppl1.

Study selection and data collection process

Studies were selected for inclusion in a two-stage process using predefined criteria. The full literature search results were screened independently by at least two reviewers (JC, EL, AO & SB) in order to identify all citations that may potentially meet the inclusion criteria, following which the full manuscripts of all selected citations were retrieved and assessed, again by two reviewers, against the inclusion criteria. Studies published as abstracts or conference presentations were only included if sufficient details to allow an appraisal of the methodology and an assessment of the results to be undertaken could be obtained. Study authors were contacted for missing information and authors of the abstracts published after 2015 were contacted if there were insufficient details to allow its inclusion in the review. Where authors did not respond, only abstracts with enough details of study participants, intervention and results were included. Where studies included a proportion of ineligible lung diseases, or where diagnoses were unclear, we contacted the authors for further information and only included these studies if this information became available. A list of potentially relevant but excluded studies is provided in online Suppl2. An inclusion flow chart and data extraction sheet were developed and used for each paper assessed. All data extraction was conducted independently by at least two reviewers. Disagreements were resolved by consensus or, if necessary, through arbitration by a third reviewer.

Data items

Data extracted included authors, intervention, comparator, diagnostic criteria, study design, quality rating and summary of results.

Risk of bias in individual studies

In assessing study quality, we used the Cochrane risk of bias tool [9] for RCTs and controlled clinical trials (CCT), with the risk of selection bias used to establish the overall risk of bias for each study. We used tools developed by the National Institute for Health, National Heart, Lung and Blood Institute (NIH NHLBI) to assess the quality of other prospective studies, including cohort studies [10].

Summary measures, synthesis of results and analysis

Studies were synthesised through a narrative synthesis, with tabulation of the results of included studies. Data were combined using Review Manager (RevMan, Version 5.3). [11]

Studies were examined for clinical, methodological and statistical heterogeneity. Only if sufficient homogeneity existed, meta-analysis was considered appropriate. If data permitted meta-analysis, we assessed statistical heterogeneity of the pooled effect size using the I-squared statistic, the chi-square test for heterogeneity, and through a visual inspection of forest plots. Possible reasons for heterogeneity were explored, and fixed effects and random effects meta-analyses were undertaken as appropriate. The choice of model was determined by the degree of heterogeneity, as judged by the I^2 statistic and p value for the chi-squared test (a random effects model was used if $P<0.10$ and/or $I^2 >50\%$).

Dichotomous outcome data were expressed as odds ratios or risk ratios. Continuous outcome data were expressed as mean differences or standardised mean differences as appropriate. For continuous variables, we considered presenting the results for end-point data or for the change from baseline. All meta-analyses were presented in forest plots, with point estimates and measures of variance (95% confidence intervals).

Results

Study selection

The updated searches identified 18,133 publications after removal of duplicates. Titles/abstracts of these publications were screened for eligibility resulting in exclusion of 17,902. 231 full-text articles were assessed for eligibility. Of these, 58 records (30 studies) were included in data synthesis. The reasons for exclusions of the remaining 173 articles are detailed in Figure 1. 18 records (17 studies) were included from the previous reviews. In total, we included 47 primary studies reported in 76 articles (Figure 1).

Study characteristics and risk of bias

A detailed summary of study characteristics is included in online Suppl3. 22 (46.8%) studies were RCTs, three (6.4%) were CCTs, 20 (42.3%) were before and after studies and two (4.3%) were cohort studies.

The included studies analysed 2,510 participants in total, 27% to 85% were males, and mean ages from 54-86 years. 33 studies included only people with IPF [12-44]. Of the remaining studies, 23% to 85% had IPF and 7% to 46% NSIP (where reported). The mean percentage predicted FVC ranged from 49.8%-103.6%, and the 6MWD from 71 to 906 metres.

22 (46.8%) studies assessed 11 different pharmacological interventions [12-18, 20-25, 39, 42, 43, 45-50]. 25 (53.2%) studies assessed non-pharmacological interventions. Pulmonary Rehabilitation or exercise training (PR) was evaluated in 22 studies [27-32, 34-37, 40, 41, 44, 51-59], while three studies used other non-pharmacological interventions [2, 26, 38].

Among 22 studies that assessed pharmacological interventions, the comparator was placebo in 10 (45.5%) studies [13, 14, 21-23, 39, 42, 45, 48, 49], while in three (13.6%) studies the comparator was another treatment [17, 25, 43]. In six (27.3%) studies, there was no control group [12, 15, 18, 20, 24, 46], while one (4.5%) study had a healthy control group [16]. One study that assessed pharmacological interventions had room air as the control [47], while another study had “no oxygen” as control [50].

Three studies compared non-pharmacological complex interventions with usual care [2, 26, 38]. Among 22 studies that assessed pulmonary rehabilitation or exercise training (PR), one study compared PR in participants with IPF to PR in those with other ILD diagnoses [54], while another study compared PR in participants with IPF to those with sarcoidosis [31]. One study compared PR in participants with IPF to PR in those with COPD from a previous study

[58]. Eleven (50%) PR studies had no control group. Three (13.6%) studies compared PR with usual care [28, 32, 35], one study compared PR with a control group that did not involve PR or addition of new medicine [27], one study compared PR with a control group that did not involve any PR, [59] and one study compared PR with a control group that only involved regular medical treatment alone [34]. Two (9.1%) studies compared PR with another intervention [40, 41].

25 (53.2%) studies did not specify their primary outcome; 12 (25.5%) studies used 6MWD as their primary outcome [13, 22-24, 28, 32, 34, 41, 48, 52, 53, 59]; four (8.5%) studies measured cough as their primary outcome [21, 39, 42, 49]; one (2.1%) study measured Qol as their primary outcome [50] and one (2.1%) study had both Qol and 6MWD as primary outcomes [29]; four (8.5%) studies used other primary outcomes besides cough, Qol and 6MWD [2, 14, 45, 46]. None of the studies examined dyspnoea as their primary outcome.

Table 1 presents study characteristics (study size, PICOS and follow-up duration) with both a summary of risk of bias and outcomes. Online Suppl3 describes detailed PICOS characteristics of included studies, Suppl4 provides detailed baseline characteristics of included participants while Suppl5 presents a more detailed account of their quality assessment.

Table 1 Summary of studies included and their results (previous review studies in blue)

Study	Disease group (number of participants):diagnostic criteria	Study design with quality rating	Control	Summary of results
Pharmacological				
Bosentan				
Corte et al, 2014[45, 60]	IPF, NSIP(39): ATS/ERS 2002	RCT, unclear RoB	Placebo	No effect on 6MWD, dyspnoea or QoL observed. Some benefits on QoL were noted in BUILD-1 in subgroup with biopsies but these were not supported by the larger BUILD-3 study.
King et al, 2011[14]	IPF(615): ATS/ERS 2000	RCT, low RoB	Placebo	
King Jr et al, 2008 (BUILD 1)[13]/Raghu et al, 2010 (2nd paper BUILD 1)[61]	IPF(154): ATS/ERS 2000/2002	RCT, unclear RoB	Placebo	
Sildenafil				
Jackson et al, 2010[23]	IPF(29): ATS/ERS 2002	RCT, unclear RoB	Placebo	Improvement in 6MWD was observed in the uncontrolled study but this was not supported by data from the RCTs. One RCT found less deterioration in dyspnoea but this was not supported by meta-analysis. QoL scores were better preserved in the sildenafil group in one RCT.
Zisman et al, 2010[22]	IPF(180)[1]	RCT, low RoB	Placebo	
Collard et al, 2007[24]	IPF(11): ATS/ERS 2000	Before and after, fair quality	No control	
Chinese medicine				
Yu et al, 2016[25]	IPF(77): Chinese Thoracic Society criteria 2002	RCT, unclear RoB	Jinshuibao capsules	Improvement in dyspnoea but no change in 6MWD with Feiwi granules. The second RCT found improvement in anxiety and depression in the combined group compared to other groups.
Zeng et al, 2015[43]	IPF(120): not reported	RCT, unclear RoB	foot bath group:traditional Chinese and Western Medicine treatment group:traditional Chinese medicine foot bath group: combined group	
Riociguat				
Nathan et al, 2017[48]	IPF, NSIP(147):not reported	RCT, unclear RoB	Placebo	No significant improvement in 6MWD with riociguat
Hoeper et al, 2013[46]	IPF(22):not reported	Before and after, fair quality	No control	
Oxygen				
Visca et al, 2017[50, 62]	IPF(76):not reported	RCT (cross over), unclear RoB	No oxygen	One RCT found improvement in health status total score, dyspnoea and chest symptoms. By contrast, the second RCT found no improvement in dyspnoea but numbers were small.
Schaeffer et al, 2017[47]	IPF(11):not reported	RCT (cross over), unclear RoB	Room air	
Corticosteroids				
Papiris et al, 2015[15]	IPF(24): ATS/ERS 2011	Cohort study, poor quality	No control	Improvement in cough reflex sensitivity to capsaicin reported in one study. Another study found some improvement in dyspnoea in the prednisolone groups but numbers were small.
Fiorucci et al, 2008[17]	IPF(30): ATS/ERS2000/2002	Before and after, fair quality	3 arms: prednisone, prednisone +cyclophosphamide, prednisone + colchicine	
Hope-Gill et al, 2003[16]	IPF(6): ATS/ERS 2002	CCT, high RoB	Healthy control group	
Proton-pump inhibitors				
Dutta et al, 2019[42]	IPF(40)[2]	RCT, low RoB	Placebo	The RCT found a reduction in geometric mean cough frequency, daytime and night-time cough frequency, while no significant effect was observed on 24-hour cough count in the before and after study.
Kilduff et al, 2014[20]	IPF(14): ATS/ERS 2002	Before and after, fair quality	No control	
Thalidomide				
Horton et al, 2012[39]	IPF(23): HRCT or surgical lung biopsy demonstrating UIP	RCT (cross-over) unclear RoB	Placebo	Improvement in cough and cough-specific Qol.
Horton et al, 2008[12]	IPF(11): ATS/ERS 2000	Before and after, poor quality	No control	
PA 101				
Birring et al, 2016[19, 49]	IPF(23): MDT consensus	RCT (cross over), unclear RoB	Placebo	Improvement in cough frequency but not nocturnal cough, cough-specific QoL and KBILD total score.

VRP 700				
Satia et al, 2014[21]	IPF(20):not reported	RCT (cross over), unclear RoB	Placebo	Significantly increased cough frequency within 4 hours of treatment. However, there was also significant reduction in dyspnoea severity at 24 hours.
Opioids				
Allen et al, 2005[18]	IPF(11): ATS/ERS	Before and after, fair quality	No control	Improvement in dyspnoea and anxiety following subcutaneously administered diamorphine. However, the numbers were small.
Non-pharmacological				
Pulmonary rehabilitation/exercise testing				
Chehere et al, 2019[55, 63]	IPF& NSIP(19):ATS/ERS 2002, 2013	Before and after, fair quality	No control	6MWD improved immediately following the intervention but not at longer-term follow-up. Data on dyspnoea and QoL were mixed.
Nolan et al, 2018[44]	IPF(90):not reported	Before and after, poor quality	No control	
Del Castillo et al, 2017[54]	IPF(9):not reported	Before and after, poor quality	Other ILD besides IPF	
Dowman et al, 2017 [28, 64-66]	IPF(61): ATS/ERS 2011	RCT, low RoB	Usual care	
Nolan et al, 2017[56]	IPF(67), NSIP (14):not reported	Before and after, poor quality	No control	
Jarosch et al, 2016[32, 67, 68]	IPF(51):not reported	RCT, low RoB	Usual care	
Keyser et al, 2015[57, 69]	IPF & NSIP (13):not reported	Before and after, fair quality	No control	
Rastogi et al, 2015[51]	IPF & NSIP(22):not reported	Before and after, fair quality	No control	
Strookappe et al, 2015[31]	IPF(12): ATS/ERS 1999, 2013	Before and after, fair quality	Sarcoidosis group	
Arizono et al, 2014[27]	IPF(48): ATS/ERS 2002	Prospective cohort study, fair quality	Without PR or addition of new medicine	
Jackson et al, 2014[59, 70]/Gaunaurd et al, 2014[33, 71, 72]	IPF(21): ATS/ERS 2011	RCT, unclear RoB	Without PR	
Rifaat et al, 2014[30, 73]	IPF(30): ATS/ERS 2011	Before and after, fair quality	No control	
Ryerson et al, 2014[53, 74-76]	IPF & NSIP(35):not reported	Before and after, fair quality	No control	
Vainshelboim et al, 2014[34, 77-82]	IPF(32): ATS/ERS 2011	RCT, unclear RoB	Regular medical treatment alone	
Holland et al, 2012[52, 83]	IPF(25):ATS/ERS 2000	Before and after, good quality	No control	
Kozu et al, 2011a[29] (overlap of participants with Kozu et al 2011b[84])	IPF(65): ATS/ERS 2000	Before and after, fair quality	No control	
Swigris et al, 2011[58]	IPF(14): ATS/ERS 2000	Before and after, fair quality	COPD group	
Ozalevli et al, 2010[36]	IPF(15): ATS/ERS 2000	Before and after, fair quality	No control	
Rammaert et al, 2009[37]	IPF(13): IPF:ATS/ERS 2000	Before and after, fair quality	No control	
Holland et al, 2008[41][a]	IPF(34): ATS/ERS 2000	RCT, low RoB	Telephone support	
Jastrzebski et al, 2008[40]	IPF(30): ATS/ERS 2000/2002 (50 yrs and above)Lung biopsy (< 50 yrs)	CCT, high RoB	General body conditioning group	
Nishiyama et al, 2008[35]	IPF(28): ATS/ERS 2002	RCT, low RoB	Usual care	
Case conference				
Bajwah et al, 2015 [2]	IPF, NSIP(47): ATS/ERS 2000	RCT, low RoB	Usual care	Improvement in palliative care outcomes, QoL and anxiety and depression scores. Qualitative findings supported these data.
Disease Management Programme				
Lindell et al, 2010[38]	IPF(19):not reported	RCT unclear RoB	Usual care group	Quantitative analysis suggested the intervention negatively affected perceptions of physical QoL. Qualitative analysis found participants valued the intervention and did not feel isolated.
Patient and Partner Empowerment Programme				
van Manen et al, 2017[26, 85]	IPF(13): ATS/ERS 2011	CCT, high RoB	Medical treatment alone	No improvement in health status, dyspnoea or HRQoL at 3 weeks and at 3 months.

IPF defined by consensus criteria; advanced stage defined as a diffusing capacity for carbon monoxide of < 35% of the predicted value.[2]IPF considered the most likely diagnosis by the regional ILD MDT; cough; radiological features of honeycombing HRCT scanning; bibasal inspiratory crackles on auscultation and features of a restrictive ventilatory defect (VC) <90% predicted and/or transfer factor for carbon monoxide (TLco) <90% predicted). In assessing study quality, we used the Cochrane risk of bias (ROB) tool for RCTs and controlled clinical trials, with the risk of selection bias (i.e random sequence generation and allocation concealment) used to establish the overall risk of bias for each study. Where both random sequence generation and allocation concealment were rated low, the study was given a 'low' RoB; where either random sequence generation or allocation concealment was rated unclear, the study was given an unclear RoB; where both random sequence generation and allocation concealment were rated high, the study was given a 'high' RoB. Other prospective studies were rated as 'good', 'fair', or 'poor' quality depending on the number of items rated positively. For before and after studies, where three items or less were rated positively, a rating of 'poor' was given; where four to seven items were rated positively, a rating of 'fair' was given; where eight items or more were rated positively, a rating of 'good' was given. For cross sectional studies, where six items or less were rated positively, a rating of 'poor' was given. ATS/ERS: American Thoracic Society/ European Respiratory Society; CCT: Controlled Clinical Trial; DLCO: Diffusion Capacity of the Lung for Carbon monoxide; FVC: Forced vital capacity; ILD: Interstitial Lung Disease; IPF: Idiopathic pulmonary fibrosis; NR: not reported; NSIP: non specific interstitial pneumonia; PPEP: Patient and Partner Empowerment Programme; RCT: randomised controlled trial; RoB: risk of selection bias; SD: Standard Deviation; UIP: Usual Interstitial Pneumonia, VC vital capacity, HRCT- High-resolution chest computed tomography. [a] data from study author

Main findings

Detailed results are available in online Suppl 6 with a summary of the main findings presented here.

Pharmacological interventions. Intervention, compared to, with f/u

Bosentan

Bosentan was assessed in three RCTs (reported in 5 papers [13, 14, 45, 60, 61]) and 808 participants: BUILD 1 [13, 61] showed no benefit of bosentan orally twice daily (62.5mg up titrated to 125mg twice daily after 1 month) compared with placebo for 6MWD or dyspnoea in 154 participants followed up to 12 months. These findings were supported by a second larger RCT (BUILD 3) with 616 participants.[14] BUILD 1 [13] found no difference for any domain of the SGRQ at 12 months, 42% of bosentan treated participants had an improved SF-36 health transition score compared with 28% of placebo (p=0.084). Subgroup analysis of participants who had undergone diagnostic biopsy however favoured bosentan showing a significant beneficial effect on Qol with mean total SGRQ scores favouring bosentan. [61] Significant treatment effects were observed at 12 months in the impact domain of the SGRQ (median treatment effect (MTE) -7.0 p=0.03), physical functioning (MTE 9.3 p=0.04), general health (MTE=9.4 p=0.01) and role emotional domains of the SF-36 (MTE 0.0 p=0.04).[13] However, none of these findings were supported in the larger BUILD 3 study.[14] A third RCT reported in two papers [45, 60] in 39 participants receiving similar doses of bosentan or placebo for 16 weeks, found no statistically significant difference in 6MWD or Qol.

Sildenafil

In the review by Bajwah et al[4], sildenafil was assessed in four studies (1 before and after study [24] and two RCTs[22, 23], of which one of the RCTs [22] was followed by an open label study) and 378 participants: the before-and after study [24] found a significant mean (90% CI) improvement in 6MWD of 49.0m (95% CI 17.5 to 84.0) in 11 participants (receiving between 20 and 50mg sildenafil three times daily for 12 weeks). However, meta-analysis of data from the two RCTs [22, 23] with 209 IPF participants did not support this finding (effect size 5.25 (95% CI −8.90 to 19.40) I^2= 56% p=0.467. One RCT[22] showed less deterioration in the sildenafil group (receiving 20mg three times daily for 12 weeks) compared to the placebo group but overall benefit was not supported by meta-analysis of data from Zisman et al and Jackson et al: effect size 5.25 (95% CI -8.90 to 19.40), I^2, p=0.129.

Zisman et al [22] found that SGRQ total score remained stable in the sildenafil group (receiving 20mg three times daily for 12 weeks) whilst worsening in placebo group (mean difference [95% CI] -4.08 [-7.3, -0.86]). The SF-36 general health sub score was better preserved in sildenafil group than placebo (mean difference [95% CI] 2.86 [0.76, 4.95]). This was not seen during the 12-week open label phase.

Traditional Chinese Medicine (TCM)

TCM was assessed in two RCTs [25, 43] and 197 participants: one RCT [25] assessed the therapeutic effects of Feiwei granules in 77 participants. The intervention group (n=62) received Feiwei granules twice a day for 6 months, while the control group (n=15) received Jinshuibao capsules, also a TCM. Participants were followed up for 6 months. Dyspnoea and SGRQ total score were significantly worse in the Feiwei granules group at baseline, and between group change in dyspnoea scores from baseline to three months was not significant (TCM group mean difference (SD) -0.6 (0.7), control group mean difference (SD) -0.3 (0.7); p = 0.111). However, between group change in dyspnoea scores from baseline to six months (TCM group mean difference (SD) -0.8 (0.8), control group mean difference (SD) 0.1 (1.0); p = 0.001) and from three months to six months (TCM group mean difference (SD) -0.2 (0.7), control group mean difference (SD) 0.3 (0.7); p = 0.009) showed significant improvement in the intervention group. SGRQ total score change from baseline to three months also showed significant improvement (TCM group mean difference (SD) -8 (14), control group mean difference (SD) -1 (6); p = 0.011). There was no difference in change in 6MWD from baseline to three months (TCM group mean difference (SD) 17 (124), control group mean difference (SD) 19 (38); p > 0.05), baseline to six months (TCM group mean difference (SD) 48 (107), control group mean difference (SD) 30 (54); p > 0.05) and from three months to six months (TCM group mean difference (SD) 31 (82), control group mean difference (SD) 11 (41); p > 0.05). The other RCT[43] evaluated the impact of TCM foot bath combined with traditional Chinese and Western medicine nursing in 120 participants. Zeng et al 2015[43] randomly assigned participants to four groups. There was significant improvement in anxiety and depression of participants in the combined group (traditional Chinese and Western Medicine nursing + TCM foot bath) compared to individual treatments at six months ($p<0.05$).

Riociguat

Riociguat was assessed in one RCT [48] and 1 before-and-after [46] study and 169 participants: Hoeper et al[46] carried out a small study involving 22 participants and found a non-significant increase in 6MWD (difference (SD): 25 (64), 95% CI -8 to 58) at 12 weeks in those receiving riociguat three times daily. Authors stated that no significant changes compared with baseline were seen for other relevant outcomes but no data were presented. Nathan et al [48] conducted a RCT involving 147 participants receiving either riociguat three times daily for 26 weeks or placebo. No significant improvement was noted in 6MWD for the intervention group at 26 weeks (MD 21 m, 95% CI: -9 to 52; p>0.2).

Ambulatory oxygen

Oxygen was assessed in two studies (both cross-over RCTs) and 87 participants: Visca et al [50, 62] compared two weeks of ambulatory oxygen to no ambulatory oxygen in 76 participants with fibrotic ILD. Health status measured by the King's Brief Interstitial Lung Disease Questionnaire (KBILD) was significantly improved in the intervention group for the total score (MD 3.7; 95% CI 1.8, 5.6; p<0.0001), breathlessness and activity domain (MD: 8.6; 95% CI 4.7, 12.5; p<0.0001) and chest symptoms (MD: 7.6; 95% CI 1.9, 13.2; p=0.009) but not for psychological symptoms. Significant improvements were also seen on the University of California San Diego shortness of breath questionnaire (p<0.0001) and St George's Respiratory Questionnaire (SGRQ) total score (p=0.018); Schaeffer et al [47] compared oxygen with room air (duration and length of follow up not reported) in 20 enrolled participants (11 with IPF), and did not find any significant difference in dyspnoea. However, it is unclear how many participants were included in analysis.

Corticosteroids

Corticosteroids were assessed in three non-randomised studies [16, 17] [15] and 60 participants. Hope-Gill et al [16] conducted a small open label study of prednisolone (40-60mg/day for at least 4 weeks) in six participants with capsaicin-induced cough and found a significant reduction in mean (SE) VAS score from 7.2 (0.8) to 2.2 (2.5) at 4 weeks (p<0.05). Fiorucci et al [17] conducted a 3-arm before and after study of 30 participants receiving prednisolone alone (group 1), prednisolone and cyclophosphamide (group 2) and prednisolone and colchicine (group 3) for 18 months. There were significant improvements in dyspnoea in the prednisolone and colchicine group compared to the other two groups. Baseline dyspnoea mean (SD) was 8.4 (2.5) versus 18 months 6.3 (2.2) (P=0.001). Two participants of group 1 (18%), one patient of group 2 (11%) and eight participants of group 3

(80%) showed a significant decrease in dyspnoea (p=0.001). Papiris et al [15] conducted a cohort study of 24 participants and found no difference in 6MWD between participants with an acute exacerbation of IPF 'ever treated' and 'never treated' with steroids. The follow up duration was not stated.

Proton pump inhibitor (PPI) therapy

PPI therapy was assessed in two studies (1 RCT [42] and 1 before and after study [20]) and 68 participants: The before and after study [20] assessed the effects of omeprazole 40 mg BD or lansoprazole 30 mg BD, plus ranitidine 300 mg at night for eight weeks in 14 participants. The median 24-hour cough count showed a non-significant increase from baseline (p = 0.7). The matched placebo RCT assessed the effects of 20mg omeprazole twice daily in 40 participants. This study found that geometric mean cough frequency at the end of treatment, adjusted for baseline, was 39.1% lower (95% CI 66% lower to 9.3% higher) in the omeprazole group compared with placebo. Similar results were obtained for daytime and night-time cough frequency. There was no clinically meaningful difference for patient-reported symptoms of cough and reflux. There was no significant difference in change in 6MWD.

Thalidomide

Thalidomide was assessed in two studies (an open label prospective cohort trial and a cross-over RCT [12, 39]) and 34 participants. Horton et al [12] presented data in 11 participants with chronic cough caused by IPF. There was marked to complete resolution of cough in 10 participants who received thalidomide administered daily in 100-400mg doses for 3 months. SGRQ data showed significant decrease on the cough question from baseline 4.9 (0.3) to 2.2 (1.6) at three months (p=0.03). A cross-over RCT of 23 participants was conducted by Horton et al (37) where 50mg (increased to 100mg after two weeks if no improvement in cough) of thalidomide was administered orally once daily for 12 weeks in a cross-over design with a two week washout. There was a significant improvement in cough-specific Qol MD (95% CI) -11.4 (-15.7 to -7.0)(p<0.001) for those taking thalidomide compared to placebo.

PA101 (cromolyn sodium)

PA101 was assessed in one crossover placebo controlled RCT [19, 49] and 23 IPF participants. 40mg PA101 (cromolyn sodium) was administered via a high-efficiency nebuliser three times daily for 14 days with washout for 14 days before crossover. The

intervention group had significantly reduced cough frequency (ratio of least-squares (LS) means 0.67, 95% CI 0.48, 0.94; p = 0.0241) but nocturnal cough, cough-specific QoL and KBILD total score were not significantly improved.

VRP700

VRP700 was assessed in one crossover placebo RCT [21] and 20 participants. Participants with cough received either a single inhaled dose of VRP700 (100mg) or placebo as a single dose intervention with a 7 day washout. VRP700 significantly increased cough frequency within four hours of treatment compared to placebo (136.8 (95% CI 80.3, 233.1) vs. 64.9 (95% CI 38.1, 110.6); p < 0.001). Reported cough severity and urge to cough were not significantly different. The authors state dyspnoea severity at 24 hours was significantly better in the VRP700 group but the data was not presented.

Opioids

Opioids were assessed in one before-and-after study [18] and 11 participants: Allen et al [18] administered single subcutaneous diamorphine doses to 11 IPF participants and showed a substantial fall in dyspnoea score from mean (SD) baseline 83(13) to 36 (11) at 15min and 36(12) at 30min (p<0.001). The authors also reported decreased observed anxiety (no details given).

Non-pharmacological interventions

Pulmonary rehabilitation and exercise training

Pulmonary rehabilitation or exercise training (PR) were assessed by 22 studies (6 RCTs [28, 32, 34, 35, 41, 59], 1 controlled clinical trial[40], 1 prospective cohort study [27] and 14 before-and-after studies [29-31, 36, 37, 44, 51-58]) with 748 participants in total. Among studies assessing PR, six had participants with severe disease (DLCO % pred < 45) [31, 37, 40, 55, 57, 59], while one study comprised a mixture of participants with severe and non-severe disease.[29]

The Cochrane review [6] included five RCTs measuring dyspnoea and combined three of these in a meta-analysis. These were screened and relevant data were extracted. We identified five additional controlled trials with new data on dyspnoea of which only one could be added to the three RCTs retrieved from the Cochrane meta-analysis, and one prospective cohort study; this was considered inappropriate, as a large proportion of evidence would be omitted.

The PR studies assessed dyspnoea using seven different scales. These included four uni-dimensional scales such as the Borg scale [86] and modifications of it, activity domain of the St George's Respiratory Questionnaire (SGRQ)[87], dyspnoea domain of the Chronic Respiratory Disease Questionnaire (CRDQ) [88] and the Oxygen Cost Diagram (OCD)[89] as well as three multi-dimensional scales including Baseline/Transition Dyspnoea Index (BDI/TDI) [90], the Medical Research Council (MRC) scale [91] and modifications of it, and the University of California St. Diego Shortness of Breath (UCSD SOB) questionnaire [92].

Of the seven controlled studies, three had inconsistent results from the different dyspnoea scales they used [28, 34, 41] while one study [35] found no significant improvement. The remaining three studies did not report any significant between-group difference [32, 40, 59]. 12 before and after studies [29-31, 36, 37, 44, 51-56] assessed dyspnoea. One study [29] found significant differences in the magnitude of change in dyspnoea immediately after PR in participants with MRC dyspnoea grades 2,3, and 5 but not in participants with MRC dyspnoea Grade 4. No significant improvement was found on longer follow-up. Five of these studies [30, 36, 44, 54, 56] found a statistically significant improvement in dyspnoea immediately after the intervention but did not assess its long-term sustainability. Chehere et al[55] used one uni-dimensional (Borg scale [86] and one multi-dimensional (BDI/TDI) [90] to assess dyspnoea and found contrasting results: Results from the BDI/TDI showed significant improvement while that with the Borg scale was not significant. Three other studies [31, 37, 51] found no significant improvement in dyspnoea. Only two studies [52, 53] reported longer follow-up (6 months) with inconsistent results.

Six RCTs measured HRQoL immediately following PR [28, 32-35, 41], while four of these studies involved longer follow-up [28, 32, 33, 41]. However, meta-analysis was considered inappropriate. Overall, results were inconsistent with some RCTs finding no statistically significant improvement effect. Longer follow-up showed PR had no significant improvement effect. Ten before-and-after studies measuring HRQoL [29, 30, 36, 37, 44, 53-56, 58] showed inconsistent findings.

A statistically significant difference between PR and control was found for change in 6MWD immediately following the intervention (n = 6 studies with 200 participants, MD 39.85 m, 95% CI 18.17 to 61.53, I^2 48%, Random effects) Figure 1. At longer-term follow-up (3 or 6 months), there was no significant difference in change in 6MWD between groups (n = 4 studies with 147 participants, MD 5.26 m, 95% CI -12.88 to 23.40, I^2 6%, Fixed effects)

Figure 2. 11 of the 14 before-after studies reported 6MWD; most studies found improvement in 6MWD immediately following PR. Only three studies [52, 53, 84] reported longer (6-month) follow-up and results were contradictory.

Case conference

One fast-track RCT [2] evaluated the effects of a palliative care case-conference in 53 participants. The intervention was a multi-professional, holistic case-conference including symptom control and developing a home-based nurse-led individualised care plan. Mean (SD) Palliative Care Outcome scores at 4 weeks were -5.7 (7.5) fast-track vs -0.4 (8.0) control, (mean change difference between the two arms was -5.3 (95% CI: -9.8, -0.7) (p=0.02); effect size (95%CI) -0.7 (-1.2, -0.1). The secondary outcomes of Qol, anxiety and depression were superior in the intervention arm, and none were worse. Qualitative findings corroborated these data.

Patient and Partner Empowerment Programme (PPEPP)

A controlled clinical trial [26, 85] evaluated the effect of a short multidisciplinary empowerment programme, PPEPP in 23 participants. Results showed no statistically significant change in health status, dyspnoea or HRQoL at 3 weeks and at 3 months.

Disease management programme

One RCT [38] evaluated a disease management program in 19 participants with mixed results. Quantitative analysis showed the intervention negatively affected perceptions of physical Qol and a tendency for greater anxiety. The mean end Beck Anxiety Index scores for the intervention were 15.13 (6.92) and control were 8.56 (6.95) (p=0.077) reflecting a non-significant increase in anxiety in the intervention group. Mean (SD) end score for the SF-36 physical component showed a statistically significant difference, intervention 31.06 (4.61) versus control 36.04 (4.63) p=0.038, reflecting a negative impact on perceptions of physical health related Qol. However, qualitative analysis found participants valued the intervention and did not feel isolated.

Adverse events

Adverse events were reported in 15 studies assessing pharmacological interventions, namely, oxygen, bosentan, corticosteroids, opioids, proton pump inhibitors, PA101, riociguat,

sildenafil and thalidomide [12-15, 17, 22-24, 39, 42, 45, 46, 62, 93, 94] (see online Suppl7 for details). In particular, seven studies described serious adverse events in studies of bosentan [13, 14, 45] sildenafil [22], thalidomide [39], riociguat [46] and oxygen [50] while three studies reported deaths in studies of corticosteroids [15], bosentan [45] and oxygen [50]. Birring et al [49] and Yu et al[25] reported that there were no serious adverse events in studies of cromolyn sodium and Feiwei granules respectively. Five PR studies reported that there were either no serious adverse events [34, 57] or no adverse events [29, 36, 41] at all.

Discussion

We have conducted the most comprehensive evidence synthesis to date providing up to date evidence on pharmacological and non-pharmacological interventions to improve symptom control, functional exercise capacity and Qol for people living with fibrotic ILD. To aid reflection on the evidence base for practitioners, policy makers and researchers, we have mapped our findings on an evidence gap map (Figure 4).

Pharmacological

The most tested pharmacological interventions were bosentan and sildenafil. Data on pharmacological interventions to improve symptoms – particularly dyspnoea continue to be limited. Of the drug studies, there were only four studies (n = 106 participants) with a primary outcome of cough [19, 21, 39, 42], and no study with a primary outcome of dyspnoea.

Interestingly, current ILD clinical guidelines [7, 95] recommend the use of a number of pharmacological measures (including opioids and benzodiazepines) for symptomatic management of ILD despite limited evidence in this group. However, a recent important study by Faisal et al[96] suggests that despite very different pathological processes, ILD and COPD patients' perceptual responses (including intensity and quality) to dyspnoea are similar. In addition, there are likely to be common mechanisms of dyspnoea. Therefore, we would suggest that it is reasonable to extrapolate evidence of effectiveness of pharmacological measures that act centrally to improve dyspnoea (eg opioids and benzodiazepines) from COPD to ILD. However, we would recommend a word of caution- whilst evidence of effectiveness may be transferred, this does not mean that safety profiles of the drugs are the same in both populations- as demonstrated by analyses of opioids and benzodiazepines safety data in COPD[97] and ILD.[98]

The British Thoracic Society recently endorsed the occasional use of oxygen by specialist teams when breathlessness is unresponsive to all other treatment [99]. This review shows there is now some evidence for oxygen in improving symptoms and Qol in ILD patients who desaturate on exercise. However, it remains unclear if oxygen is any more effective than non-pharmacological interventions such as fans or cognitive behavioural therapy. In light of the many negative psychological, social and financial aspects of oxygen, further research is needed before widescale adoption of oxygen in this group.

Non-pharmacological

As shown by Figure 4, the most tested intervention and for which there is the strongest evidence base was PR with 47% of all studies being PR related. Studies with PR achieved short-term improvements in 6MWD. This contrasts with COPD where a reduction in dyspnoea is more consistent.[100] The difference in effect for PR in ILD may be related to the more fluctuating and declining nature of the disease. Among studies assessing PR, six had participants with severe disease (DLCO, % pred < 45) [31, 37, 40, 55, 57, 59] while one study comprised a mixture of participants with severe and non-severe disease.[29] Participants with more advanced disease may be less able to participate in PR and therefore it is unreasonable to expect to see the improvement seen in COPD. In ILD, the more appropriate outcome is preservation in symptoms and Qol rather than improvement per se. Whilst no clear improvement in symptoms and Qol of life is seen, a slowing of deterioration in rapidly depreciating disease or the attainment of individualised goals are more meaningful clinical outcomes.[101] We attempted to analyse rate of deterioration of outcomes but were unable to do so, limited by the values presented. Furthermore, a plethora of dyspnoea assessment tools limited generalisability. A total of 37 studies assessed dyspnoea using 10 different scales. Of these, 19 studies were in PR using seven different scales to measure dyspnoea. As noted by Similowski [102], dyspnoea is a complex and multi-dimensional experience that warrants a multi-dimensional tool to assess the effect of complex interventions. PR may be having a positive effect on the affective dimensions of dyspnoea which are not captured by uni-dimensional tools focussing on the symptom of dyspnoea alone (eg VAS). In contrast, multi-dimensional tools (eg CRDQ) assess the impact of dyspnoea on various domains such as activities of daily living, emotional and mental functioning, sense of mastery or other person related outcomes. Of note, for the 19 PR studies that assessed dyspnoea, four unidimensional and three multidimensional dyspnoea measures were used. A review of breathlessness tools by Bausewein et al [103] notes that there is no one scale that can accurately reflect the far-reaching effects of breathlessness in a patient with advanced disease. They recommend combining a uni-dimensional scale with either a disease-specific scale or a multi-dimensional scale in conjunction with other methods such as qualitative methods to fully gauge psychosocial impact of interventions to improve dyspnoea. In this evidence synthesis, only seven PR studies used both unidimensional and multidimensional measures.

Recommendations

The evidence gap in Figure 4 demonstrates graphically that dyspnoea is the most researched symptom and cough, the least. Research now needs to focus on pharmacological interventions to improve neglected symptoms such as cough whilst ensuring that dyspnoea is prioritised as a primary end point for future studies.

The ongoing presentation of limited data and focus on improvement of outcomes is leading to discounting of the effectiveness of interventions. Given the problem of powering and the multiplicity of uncertainties listed above, an international consensus is needed on the goals of palliative interventions, the ranking of candidate primary end-point in each domain and the selection criteria for studied populations. Failure to reach such consensus may lead to similar difficulties to those in studies of acute IPF exacerbations and ILD associated with occult connective tissue disease. In both areas, lack of standardisation hindered integrating a decade of published data into an evidence base. In both areas, international consensus statements were formulated to confront fragmentation of research. Based on this review, research into palliative care in ILD is arguably in danger of following the same pathway. We call for a major initiative, starting with a Delphi exercise, to agree on an ongoing research agenda.

Strengths and limitations

Strengths of this work include a registered protocol, and a systematic and comprehensive search across multiple databases, inclusive of grey literature, with no exclusions by publication year. All screening, eligibility, data extraction and quality assessment was conducted independently by two authors, and multiple stakeholders (researchers, clinicians and patient representative) contributed to the analysis and interpretation of these data. In addition, we have for the first time, clearly mapped the evidence gap to provide a visual overview of the evidence gap for types of interventions evaluated and outcomes reported. This allows the reader to explore findings and quality of the existing evidence and facilitate informed judgement and evidence-based decision making. Importantly, the evidence gap map has identified key areas where little or no evidence from research is available and where future research can be focused.

The main limitation of this review is the low quality of the studies included. Many studies were uncontrolled, with small sample sizes and unclear quality aspects. Follow-up was often

short and few interventions provided evidence that could be meta-analysed. However, we have only used high quality studies in the meta-analyses and presented studies clearly to allow readers to draw their own conclusions. To limit heterogeneity, we did not include connective tissue disease associated ILDs and it is possible that there are further relevant studies available. In addition, we included studies looking at both efficacy and effectiveness as we thought it important to assess and present both. Moreover, although we did not assess for statistical evidence of publication bias, there was evidence of selective reporting where study authors did not provide data for statistically non-significant findings.

Conclusion and clinical implications

This evidence synthesis highlights overwhelmingly that the most researched symptom is dyspnoea and the strongest evidence base is for short-term PR. The least researched symptom was cough. The research priorities going forward must focus on prioritising and standardising meaningful outcomes and focusing interventions on neglected symptoms. We call for a sea change in the way we conduct research in this area starting in the first instance with a Delphi exercise concluding in recommendations of a core outcome measure set.

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Reference List

1. Vancheri C. Idiopathic pulmonary fibrosis and cancer: do they really look similar? *BMC medicine* 2015: 13: 220-220.
2. Bajwah S, Ross JR, Wells AU, Mohammed K, Oyebode C, Birring SS, Patel AS, Koffman J, Higginson IJ, Riley J. Palliative care for patients with advanced fibrotic lung disease: a randomised controlled phase II and feasibility trial of a community case conference intervention. *Thorax* 2015: 70(9): 830-839.
3. Kreuter M, Bendstrup E, Russell AM, Bajwah S, Lindell K, Adir Y, Brown CE, Calligaro G, Cassidy N, Corte TJ, Geissler K, Hassan AA, Johannson KA, Kairalla R, Kolb M, Kondoh Y, Quadrelli S, Swigris J, Udwadia Z, Wells A, Wijsenbeek M. Palliative care in interstitial lung disease: living well. *Lancet Respir Med* 2017: 5(12): 968-980.
4. Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel AS, Koffman J, Riley J. Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature. *Thorax* 2013: 68(9): 867-879.
5. Loveman E, Copley VR, Colquitt J, Scott DA, Clegg A, Jones J, O'Reilly KM, Singh S, Bausewein C, Wells A. The clinical effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: a systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)* 2015: 19(20): i-xxiv, 1-336.
6. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database of Systematic Reviews* 2014(10): CD006322.
7. National Institute for Health and Care Excellence. Idiopathic pulmonary fibrosis in adults: diagnosis and management. Clinical Guideline (CG 163). Updated May 2017. NICE, London, 2013.
8. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, Brozek JL, Collard HR, Cunningham W, Homma S, Johkoh T, Martinez FJ, Myers J, Protzko SL, Richeldi L, Rind D, Selman M, Theodore A, Wells AU, Hoogsteden H, Schunemann HJ. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med* 2015: 192(2): e3-19.
9. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods G, Cochrane Statistical Methods G. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011: 343: d5928.
10. NHLBI N. Study quality assessment tools 2018 [cited 2018 25 January 2018]; Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
11. RevMan. [Computer program] Version 5.3. The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, 2014.
12. Horton MR, Danoff SK, Lechtzin N. Thalidomide inhibits the intractable cough of idiopathic pulmonary fibrosis. *Thorax* 2008: 63: 749-749.
13. King TE, Jr., Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stahler G, Leconte I, Roux S, Raghu G. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008: 177(1): 75-81.
14. King TE, Jr., Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, Valeyre D, Leconte I, Morganti A, Roux S, Behr J. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *American Journal of Respiratory & Critical Care Medicine* 2011: 184(1): 92-99.
15. Papiris SA, Kagouridis K, Kolilekas L, Papaioannou AI, Roussou A, Triantafillidou C, Baou K, Malagari K, Argentos S, Kotanidou A, Karakatsani A, Manali ED. Survival in Idiopathic pulmonary fibrosis acute exacerbations: the non-steroid approach. *BMC Pulmonary Medicine* 2015: 15: 162.
16. Hope-Gill BD, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003: 168(8): 995-1002.
17. Fiorucci E, Lucantoni G, Paone G, Zotti M, Li BE, Serpilli M, Regimenti P, Cammarella I, Puglisi G, Schmid G. Colchicine, cyclophosphamide and prednisone in the treatment of mild-moderate idiopathic pulmonary fibrosis: comparison of three currently available therapeutic regimens. *Eur Rev Med Pharmacol Sci* 2008: 12(2): 105-111.

18. Allen S, Raut S, Woollard J, Vassallo M. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. *Palliat Med* 2005: 19(2): 128-130.
19. Birring S, Wijsenbeek M, Al SA, Tutuncu A, Morice A. Significant improvement in refractory chronic cough with inhaled PA101 in patients with idiopathic pulmonary fibrosis: Results from phase 2 trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
20. Kilduff CE, Counter MJ, Thomas GA, Harrison NK, Hope-Gill BD. Effect of acid suppression therapy on gastroesophageal reflux and cough in idiopathic pulmonary fibrosis: an intervention study. *Cough (London, England)* 2014: 10: 4.
21. Satia I, Badri H, Dockry R, Chaudhuri N, Brown G, Abbott-Banner K, Smith JA. A randomised, double-blind, placebocontrolled crossover study to assess the efficacy of a single dose of 100 mg of VRP700 by inhalation in reducing the frequency and severity of cough in adult patients with idiopathic pulmonary fibrosis. *Thorax* 2015: 70: A52.
22. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010: 363(7): 620-628.
23. Jackson RM, Glassberg MK, Ramos CF, Bejarano PA, Butrous G, Gomez-Marin O. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. *Lung* 2010: 188(2): 115-123.
24. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest* 2007: 131(3): 897-899.
25. Yu Y, Sun Z, Shi L, Zhang Y, Zhou Z, Zhang S, Chao E. Effects of Feiwei granules in the treatment of idiopathic pulmonary fibrosis: a randomized and placebo-controlled trial. *Journal of Traditional Chinese Medicine* 2016: 36(4): 427-433.
26. van Manen MGJ, van 't Spiker A, Tak NC, Baars CT, Jongenotter SM, van Roon LR, Kraan J, Hoogsteden HC, Wijsenbeek MS. Patient and partner empowerment programme for idiopathic pulmonary fibrosis. *European Respiratory Journal* 2017: 49: 1601596 [https://doi.org/1601510.1601183/13993003.13901596-13992016].
27. Arizono S, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, Ogawa T, Watanabe F, Nishiyama O, Nishimura K, Kozu R, Tabira K. Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis. *Respiratory Care* 2014: 59(7): 1108-1115.
28. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, Glaspole I, Goh NS, Southcott AM, Burge AT, Gillies R, Martin A, Holland AE. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax* 2017: 17.
29. 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): 1196-1202.
30. Rifaat N, Anwar E, Ali YM, Ellabban A, Hasan AA. Value of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Egyptian Journal of Chest Diseases and Tuberculosis* 2014: 63(4): 1013-1017.
31. Strookappe B, Elfferich M, Swigris J, Verschoof A, Veschakelen J, Knevel T, Drent M. Benefits of physical training in patients with idiopathic or end-stage sarcoidosis-related pulmonary fibrosis: a pilot study. *Sarcoidosis Vasculitis & Diffuse Lung Diseases* 2015: 32(1): 43-52.
32. Jarosch I, Schneeberger T, Gloeckl R, Kreuter M, Neurohr C, Prasse A, Behr J, Kenn K. Effects of a 3-week pulmonary rehabilitation program in patients with idiopathic pulmonary fibrosis-a randomized, controlled trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
33. Gaunaurd IA, Gomez-Marin OW, Ramos CF, Sol CM, Cohen MI, Cahalin LP, Cardenas DD, Jackson RM. Physical activity and quality of life improvements of patients with idiopathic pulmonary fibrosis completing a pulmonary rehabilitation program. *Respiratory Care* 2014: 59(12): 1872-1879.
34. Vainshelboim B, Oliveira J, Yehoshua L, Weiss I, Fox BD, Fruchter O, Kramer MR. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. *Respiration* 2014: 88(5): 378-388.

35. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S, Nishimura K, Taniguchi H. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008: 13(3): 394-399.
36. Ozalevli S, Karaali HK, Ilgin D, Ucan ES. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Multidisciplinary Respiratory Medicine* 2010: 5(1): 31-37.
37. Rammaert B, Leroy S, Cavestri B, Wallaert B, Grosbois JM. [Home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis]. *Rev Mal Respir* 2009: 26(3): 275-282.
38. Lindell KO, Olshansky E, Song M, Zullo TG, Gibson KF, Kaminski N, Hoffman LA. Impact of a disease-management program on symptom burden and health-related quality of life in patients with idiopathic pulmonary fibrosis and their care partners. *Heart & Lung* 2010: 39(4): 304-314.
39. Horton MR, Santopietro V, Mathew L, et al. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: A randomized trial. *Annals of Internal Medicine* 2012: 157(6): 398-406.
40. Jastrzebski D, Kozielski J, Zebrowska A. [Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis with inspiratory muscle training]. *Pneumonologia i alergologia polska* 2008: 76(3): 131-141.
41. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax, 2008; pp. 549-554.
42. Dutta P, Funston W, Mossop H, Ryan V, Jones R, Forbes R, Sen S, Pearson J, Griffin SM, Smith JA, Ward C, Forrest IA, Simpson AJ. Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. *Thorax* 2019.
43. Zeng ZY. Recent study on traditional Chinese medicine foot bath combined with traditional Chinese and western medicine nursing for IPF. *Chinese community doctors [zhong guo she qu yi shi]* 2015: 31(14): 143-146.
44. Nolan CM, Maddocks M, Maher TM, Patel S, Barker RE, Jones SE, Kwan H, Mehta B, Hogg L, Tuffnell R, George PM, Cullinan P, Man WD. Improvement in Gait Speed with Pulmonary Rehabilitation Is Associated with Increased Survival in Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2018: 197.
45. Corte TJ, Keir GJ, Dimopoulos K, Howard L, Corris PA, Parfitt L, Foley C, Yanez-Lopez M, Babalis D, Marino P, Maher TM, Renzoni EA, Spencer L, Elliot CA, Birring SS, O'Reilly K, Gatzoulis MA, Wells AU, Wort SJ, Group BS. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *American Journal of Respiratory & Critical Care Medicine* 2014: 190(2): 208-217.
46. Hoeper MM, Halank M, Wilkens H, Gunther A, Weimann G, Gebert I, Leuchte HH, Behr J. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. *European Respiratory Journal* 2013: 41(4): 853-860.
47. Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, Mitchell RA, Sheel AW, Khalil N, Camp PG, et al. Effects of hyperoxia on dyspnoea and exercise endurance in fibrotic interstitial lung disease. *The european respiratory journal* 2017: 49(5).
48. Nathan S, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez F, Corte T, Keogh A, Leuchte H, Mogulkoc N, Ulrich S, Wuyts W, Malcolm S, Shah S, Yao M, Wells A. RISE-IIP: Riociguat for the treatment of pulmonary hypertension associated with idiopathic interstitial pneumonia. *European Respiratory Journal* 2017: 50.
49. Birring SS, Wijsenbeek MS, Agrawal S, van den Berg JWK, Stone H, Maher TM, Tutuncu A, Morice AH. A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial. *The Lancet Respiratory Medicine* 2017: 08: 08.
50. Visca D, Mori L, Tsipouri V, Fleming S, Firouzi A, Bonini M, Pavitt MJ, Alfieri V, Canu S, Bonifazi M, et al. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. *The lancet respiratory medicine* 2018: 6(10): 759-770.

51. Rastogi SA, Koltharkar M, Udwadia ZF. Prospective study of pulmonary rehabilitation in interstitial lung disease in resource limited setting: An Indian experience. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2015: 191(no pagination).
52. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. *Respiratory Medicine* 2012: 106(3): 429-435.
53. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, Khalil N, Collard HR, Garvey C. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respiratory Medicine* 2014: 108(1): 203-210.
54. Del Castillo NT, Paredes L, Shek N, Gutierrez HH, Betancourt-Pena J. Benefits of Pulmonary Rehabilitation in Patients With Idiopathic Pulmonary Fibrosis and Other Interstitial Lung Diseases. *Chest* 2017: 152(4): 982A-982A.
55. Chehere B, Bougault V, Chenivesse C, Grosbois JM, Wallaert B. Cardiorespiratory adaptation during 6-Minute Walk Test in fibrotic idiopathic interstitial pneumonia patients who did or did not respond to pulmonary rehabilitation. *Eur J Phys Rehabil Med* 2019: 55(1): 103-112.
56. Nolan CM, Maddocks M, Delogu V, Patel S, Barked RE, Mehta B, Hogg L, Tuffnell R, Canavan JL, Jonesi SE, Koni SS, Maher TM, Cullinan P, Man WD. Responsiveness And Minimum Clinically Important Difference (mcid) Of The 4 Metre Gait Speed (4mgs) In Fibrotic Interstitial Lung Disease. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
57. Keyser RE, Woolstenhulme JG, Chin LM, Nathan SD, Weir NA, Connors G, Drinkard B, Lamberti J, Chan L. Cardiorespiratory function before and after aerobic exercise training in patients with interstitial lung disease. *J Cardiopulm Rehabil Prev* 2015: 35(1): 47-55.
58. Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, Wamboldt FS. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. *Respir Care* 2011: 56(6): 783-789.
59. Jackson RM, Gomez-Marin OW, Ramos CF, Sol CM, Cohen MI, Gaunaurd IA, Cahalin LP, Cardenas DD. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. *Lung* 2014: 192(3): 367-376.
60. Keir G, Corte T, Parfitt L, Maher T, Marino P, Renzoni E, Dimopoulos K, Gatzoulis M, Madden B, Howard L, Corris P, O'Reilly K, Hope-Gill B, Birring S, Wells A, Wort SJ. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia: A randomized, double-blind, placebo-controlled study. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2013: 42(no pagination).
61. Raghu G, King TE, Jr., 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): 118-123.
62. Visca D, Mori L, Tsipouri V, Canu S, Bonini M, Pavitt M, Fleming S, Firouzi A, Farquhar M, Leung E, Hogben C, De Lauretis A, Kokosi M, Lee J, Lyne R, Rippon N, Chetta A, Russell AM, Saunders P, Kouranos V, Margaritopoulos G, Maher TM, Stockford A, Cullinan P, Hopkins N, Birring S, Wells AU, Whitty J, Banya W, Adamali H, Spencer L, Sestini P, Renzoni EA. Ambox: A Randomised Controlled, Crossover Trial Evaluating The Effects Of Ambulatory Oxygen On Health Status In Patients With Fibrotic Interstitial Lung Disease. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
63. Chehere B, Bougault V, Chenivesse C, Grosbois J-M, Wallaert B. Cardiorespiratory adaptation in a 6-minute walk test by fibrotic idiopathic interstitial pneumonia patients who did or did not respond to pulmonary rehabilitation. *European journal of physical and rehabilitation medicine* 2018.
64. Dowman L, McDonald CF, Hill C, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge A, Ndongo R, Martin A, Holland AE. The benefits of exercise training in interstitial lung disease: protocol for a multicentre randomised controlled trial. *BMC Pulmonary Medicine* 2013: 13: 8.
65. Dowman L, McDonald C, Hill C, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge A, Ndongo R, Martin A, Holland A. Effect of disease aetiology on response to exercise training in patients with interstitial lung disease. *Respirology* 2015: 20: 58.

66. Dowman LM, McDonald CF, Hill CJ, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge AT, Ndongo R, Martin A, Holland AE. 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: 191(no pagination).
67. Jarosch I, Schneeberger T, Gloeckl R, Kreuter M, Benstz J, Frankenberger M, Neurohr C, Prasse A, Behr J, Kenn K. Different Effects Of Pulmonary Rehabilitation In Anxious Vs. Non-Anxious Patients With Idiopathic Pulmonary Fibrosis - A Pilot Study. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
68. Schneeberger T, Glockl R, Jarosch I, Behr J, Neurohr C, Frankenberger M, Prasse A, Kreuter M, Kenn K. Effects of a 3-week inpatient pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis - a randomized, controlled trial. *Wiener Klinische Wochenschrift* 2016: 128(19-20): 779-780.
69. Keyser RE, Christensen EJ, Chin LM, Woolstenhulme JG, Drinkard B, Quinn A, Connors G, Weir NA, Nathan SD, Chan LE. Changes in fatigability following intense aerobic exercise training in patients with interstitial lung disease. *Respiratory Medicine* 2015: 109(4): 517-525.
70. Jackson R, Ramos C, Cardenas D, Sol C, Cohen M, Gaunaurd I. Effects of aerobic and strength training on symptoms and exercise capacity of IPF patients [Abstract]. European Respiratory Journal, 2012; p. 672s [P3686].
71. Gaunaurd IA, Cardenas DD, Cahalin LP, Cohen MI, Ramos CF, Jackson RM. Health-related quality of life of IPF patients in a pulmonary rehabilitation program (Abstract). American Journal of Respiratory and Critical Care Medicine, 2014; p. A2639.
72. Gomez O, Ramos CF, Cardenas D, Gaunaurd I, Eustis N, Cohen M, Jackson RM. Exercise training during pulmonary rehabilitation increases activity levels of IPF patients. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2012: 185(no pagination).
73. 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: 44(no pagination).
74. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp P, Wilcox PG, Khalil N, Garvey CM, Collard HR. Pulmonary rehabilitation improves long-term quality of life in patients with interstitial lung disease. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2013: 187(no pagination).
75. Ryerson CJ, Cayou C, Topp FJ, Hilling L, Wilcox PG, Khalil N, Collard HR, Garvey CM. Pulmonary rehabilitation in interstitial lung disease: Predictors of success. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2012: 185(no pagination).
76. Ryerson CJ, Topp F, Cayou C, Hilling L, Camp P, Khalil N, Wilcox PG, Collard HR, Garvey CM. A low baseline 6mwd predicts greater improvement from pulmonary rehabilitation in interstitial lung disease. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2013: 187(no pagination).
77. Vainshelboim B, Oliveira J, Fox B, Kramer M. Effect of exercise pulmonary rehabilitation on long-term outcomes in idiopathic pulmonary fibrosis. European respiratory journal, 2014.
78. Vainshelboim B, Oliveira J, Fox BD, Yehoshua L, Fruchter O, Kramer MR. Effect of exercise pulmonary rehabilitation on long-term outcomes in idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2014: 189(no pagination).
79. Vainshelboim B, Oliveira J, Yohoshua L, Wais I, Kramer MR. Effect of Pulmonary Rehabilitation Program on Exercise Tolerance and Functional Capacity in Patients with Idiopathic Pulmonary Fibrosis. *Medicine and Science in Sports and Exercise* 2013: 45(5): 543-543.

80. 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): 345-354.
81. Vainshelboim B, Fox BD, Kramer MR, Izhakian S, Gershman E, Oliveira J. Short-Term Improvement in Physical Activity and Body Composition After Supervised Exercise Training Program in Idiopathic Pulmonary Fibrosis. *Archives of Physical Medicine & Rehabilitation* 2016: 97(5): 788-797.
82. Vainshelboim B, Kramer MR, Fox BD, Izhakian S, Sagie A, Oliveira J. Supervised exercise training improves exercise cardiovascular function in idiopathic pulmonary fibrosis. *European journal of physical & rehabilitation medicine* 2016: 19.
83. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Benefits of exercise training are related to disease severity in idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2011: 183(1 MeetingAbstracts).
84. Kozu R, Senjyu H, Jenkins SC, 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.
85. Van Manen M, Van't Spijker A, Tak N, Baars C, Jongenotter S, Van Roon L, Kraan J, Wijsenbeek M. Patient and partner "empowerment" program in idiopathic pulmonary fibrosis (ppepp): Improving quality of life in patients and their partners. *Qjm* 2016: 109: S46.
86. Borg GA. Psychophysical bases of perceived exertion. *Medicine and science in sports and exercise* 1982: 14(5): 377-381.
87. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *The American review of respiratory disease* 1992: 145(6): 1321-1327.
88. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987: 42(10): 773-778.
89. McGavin CR, Artvinli M, Naoe H, McHardy GJ. Dyspnoea, disability, and distance walked: comparison of estimates of exercise performance in respiratory disease. *Br Med J* 1978: 2(6132): 241-243.
90. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984: 85(6): 751-758.
91. Medical Research Council. Standardized Questionaries on Respiratory Symptoms. *Br Med J* 1960: 2(5213): 1665-1665.
92. Eakin EG, Resnikoff PM, Prewitt LM, Ries AL, Kaplan RM. Validation of a New Dyspnea Measure: The UCSD Shortness of Breath Questionnaire. *Chest* 1998: 113(3): 619-624.
93. Hanada M, Sakamoto N, Ishimatsu Y, Kakugawa T, Obase Y, Kozu R, Senjyu H, Izumikawa K, Mukae H, Kohno S. Effect of long-term treatment with corticosteroids on skeletal muscle strength, functional exercise capacity and health status in patients with interstitial lung disease. *Respirology* 2016: 21(6): 1088-1093.
94. Currow DC, McDonald C, Oaten S, Kenny B, Allcroft P, Frith P, Briffa M, Johnson MJ, Abernethy AP. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *Journal of Pain and Symptom Management* 2011: 42(3): 388-399.
95. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, Hirani N, Hubbard R, Lake F, Millar AB, Wallace WA, Wells AU, Whyte MK, Wilsher ML. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008: 63 Suppl 5: v1-58.
96. Faisal A, Alghamdi BJ, Ciavaglia CE, Elbehairy AF, Webb KA, Ora J, Neder JA, O'Donnell DE. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *American journal of respiratory and critical care medicine* 2016: 193(3): 299-309.

97. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *Bmj* 2014: 348: g445.
98. Bajwah S, Davies JM, Tanash H, Currow DC, Oluyase AO, Ekström M. Safety of benzodiazepines and opioids in interstitial lung disease: a national prospective study. *European Respiratory Journal* 2018: 52(6): 1801278.
99. O'Driscoll BR, Howard LS, Earis J, Mak V. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax* 2017: 72: ii1-ii90.
100. Lacasse Y, Martin S, Lasserson T, Goldstein R. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. A Cochrane systematic review. 2007.
101. Brighton LJ, Miller S, Farquhar M, Booth S, Yi D, Gao W, Bajwah S, Man WD, Higginson IJ, Maddocks M. Holistic services for people with advanced disease and chronic breathlessness: a systematic review and meta-analysis. *Thorax* 2019: 74(3): 270-281.
102. Similowski T, Serresse L. Lessons from negative dyspnoea studies: arguments for the multidimensional evaluation of multidirectional therapeutic approaches. Eur Respiratory Soc, 2019.
103. Bausewein C, Farquhar M, Booth S, Gysels M, Higginson I. Measurement of breathlessness in advanced disease: a systematic review. *Respiratory medicine* 2007: 101(3): 399-410.

Figure 1 PRISMA Flow chart

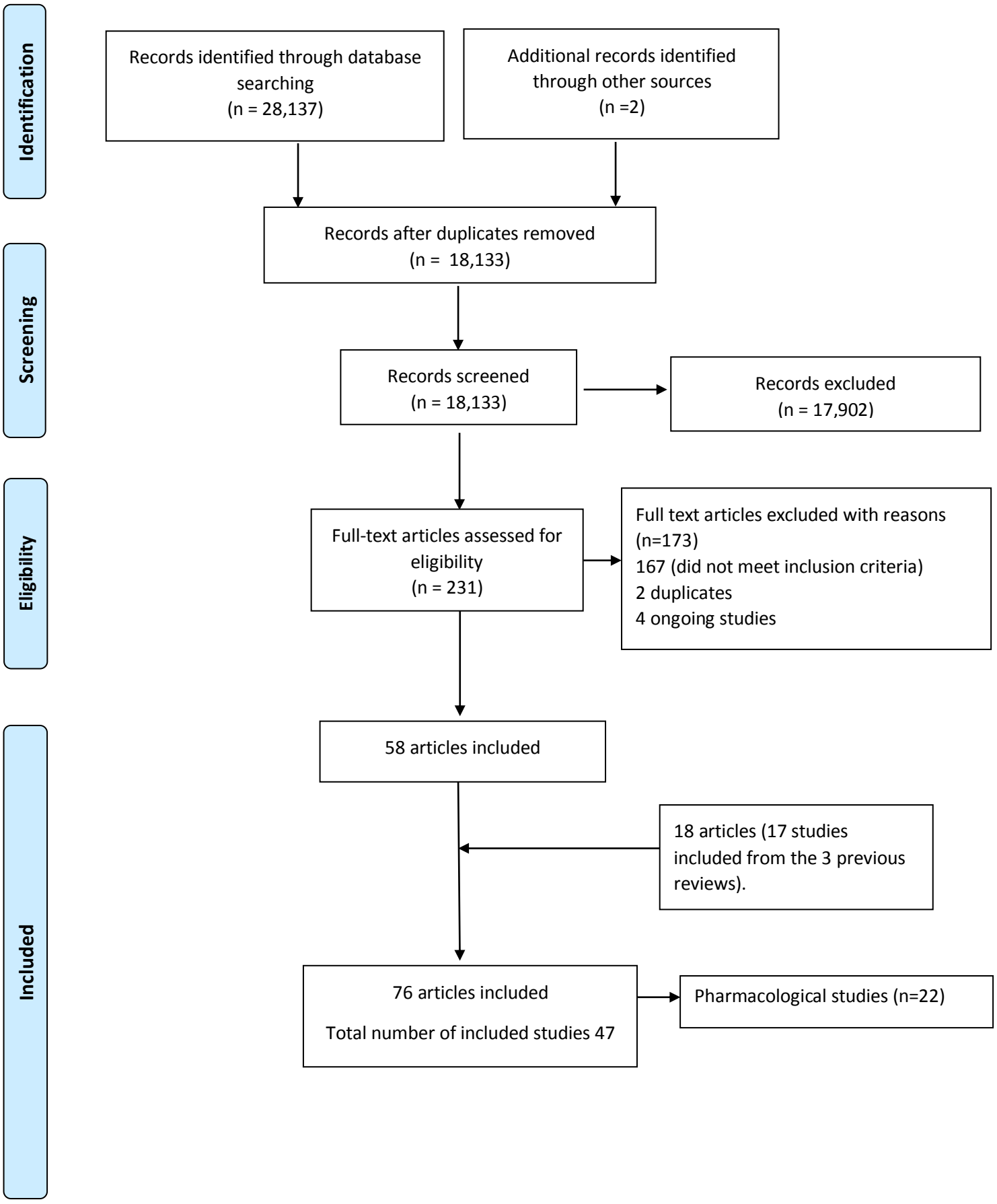


Figure 2 Meta-analysis of PR vs control for 6MWD at intervention end

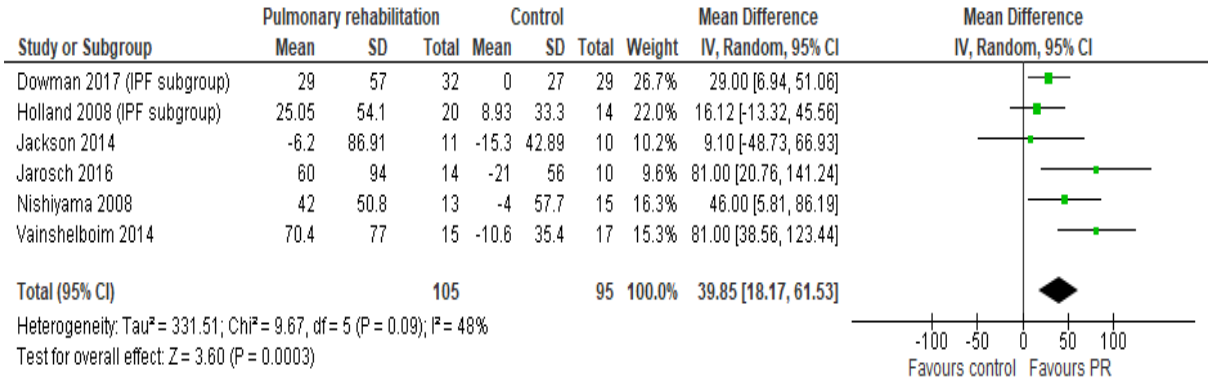


Figure 3 Meta-analysis of PR vs control for 6MWD at longest follow-up

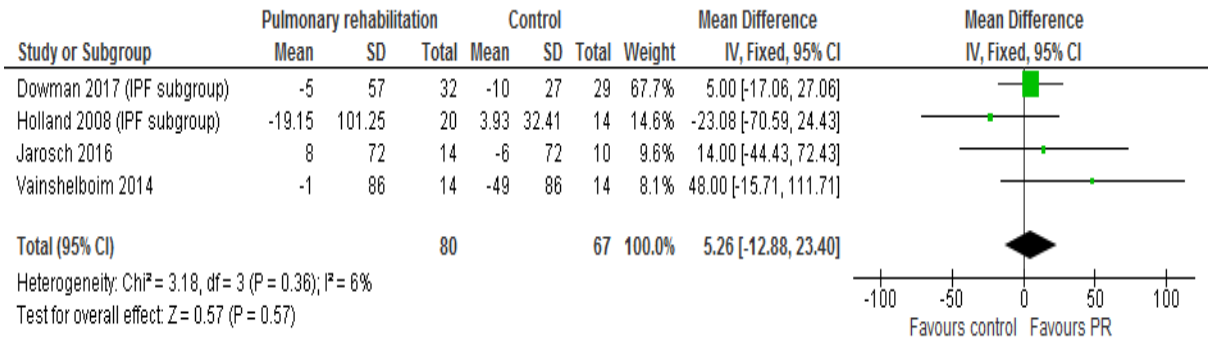
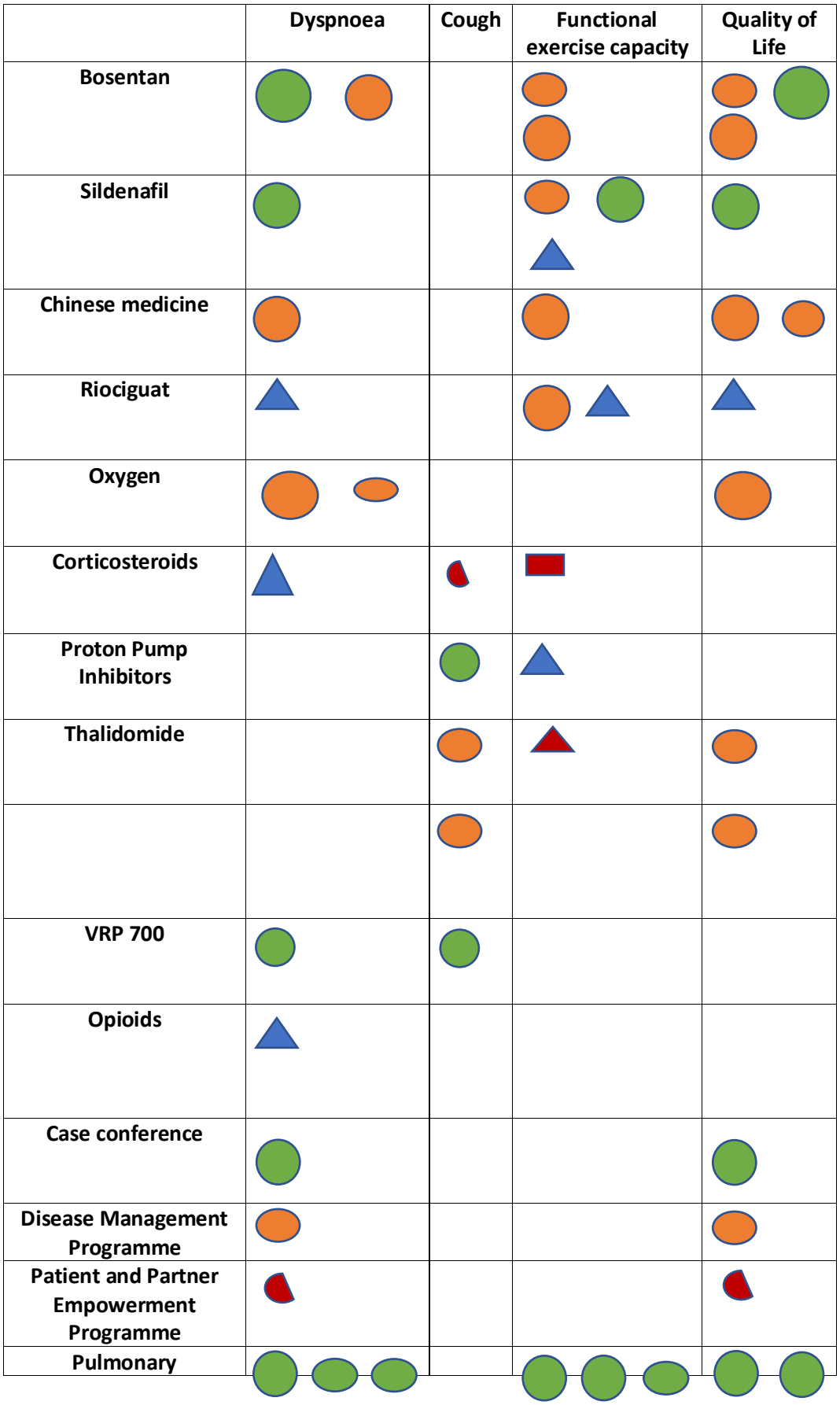
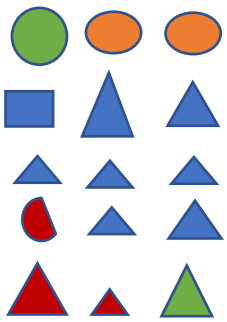
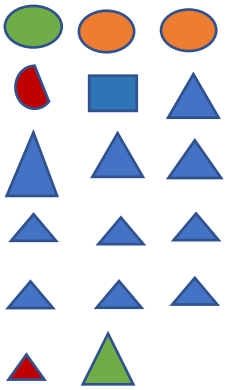
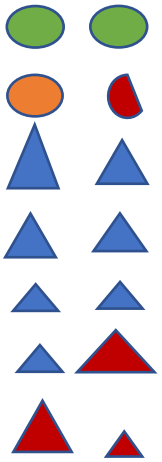
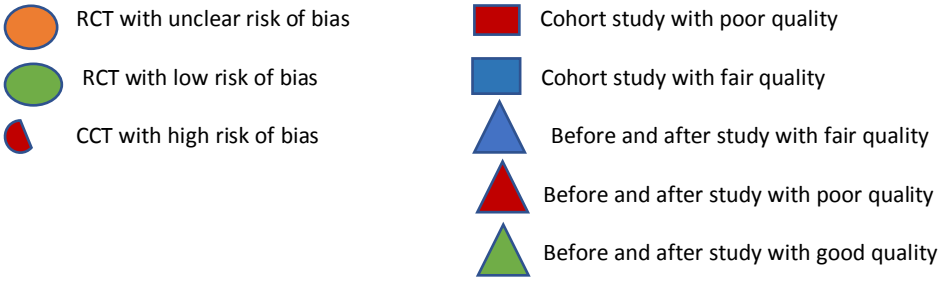


Figure 4 Evidence gap map for interventions to improve symptoms, functional exercise capacity and quality of life in ILD



rehabilitation / exercise training				

Footnote:
Shape size is an indication of the size of the study. Each shape represents a study that reported the outcome.



Suppl 1: Summary of previous reviews

Author, year, EN#	Bajwah et al, 2012[1]
Study population	People with progressive idiopathic fibrotic interstitial lung diseases (IPF, NSIP, cryptogenic fibrosing alveolitis (CFA) and idiopathic interstitial pneumonia (IIP))
Intervention(s)	Any single or combined interventions for the treatment of progressive idiopathic fibrotic ILDs, excluding lung transplantation (relevant to the present review: sildenafil, pulmonary rehabilitation, disease management programme, oxygen, diamorphine, thalidomide)
Included studies, N Reference details	Total 35. Relevant to present review: 13 (in 12 publications) *Sildenafil: (4 studies in 3 publications)* Zisman 2010, N Engl J Med; 363:620–8. Collard 2007, Chest; 131: 897-900 Jackson 2010, Lung; 188: 115-23 *Pulmonary Rehabilitation:* Nishiyama 2008, Respirology;13:394–9. Holland 2008, Thorax;63: 549–54. Ozalevli 2010, Multidisciplinary Respir Med;5: 31–7. Rammaert 2009, Rev Mal Respir; 26: 275–82. Kozu 2011, Respiration; 81: 196–205. Swigris 2011, Respir Care; 56: 783–9. *Disease management programme:* Lindell 2010, Heart Lung;39:304–13. *Diamorphine:* Allen 2005, Palliat Med; 19: 128–30. *Thalidomide*: Horton 2008, Thorax;63:749
Results (relevant outcomes)	*Sildenafil:* on 6MWD one study found a significant improvement, but a meta-analysis of two RCTs did not (5.25 (95% CI −8.90 to 19.40)). For dyspnoea there was no overall benefit from meta-analysis. Quality of life remained stable / was better preserved in the sildenafil arm of one study than in the placebo arm but this was not seen during longer follow-up. *Pulmonary Rehabilitation:* Meta-analysis showed an overall significant benefit of PR on 6MWD (2 studies, mean difference 27.4, 95% CI 4.1 to 50.7) which was supported in the non-randomised studies. Effects on dyspnoea and other symptoms were mixed with a few studies finding significant effects on dyspnoea. Four studies found significant effects on QOL, the remaining 2 studies did not. *Disease management programme:* There was mixed evidence of benefit for symptoms and QOL in the one study. *Diamorphine:* in one study there was a significant decline in dyspnoea (weak evidence). *Thalidomide*: cough and quality of life were improved (weak evidence).
Review conclusions	There is strong evidence for the use of pulmonary rehabilitation to improve 6MWD and moderate evidence for the use of sildenafil and pulmonary rehabilitation to improve QoL.

Author, year, EN#	Loveman 2015[2]
Study population	People with a confirmed diagnosis of IPF
Intervention(s)	Any available and currently used (in the NHS) interventions which aim to manage symptoms or modify IPF (relevant to the present review: thalidomide, sildenafil, disease management programme, PR)
Included studies, N Reference details	Total 14. Relevant to present review: 5. *Thalidomide*: Horton 2012, Ann Intern Med;157:398–406, Am J Respir Crit Care Med 2012;185:A3635. *Sildenafil:* Zisman 2010, N Engl J Med;363:620–8. *Disease management programme:* Lindell 2010, Heart Lung;39:304–13. *PR:* Jastrzebski 2008, Pneumonologia i Alergologia Polska 2008;76:131–41. Nishiyama 2008, Respirology 2008;13:394–9.
Results (relevant outcomes)	*Thalidomide*: One randomised crossover trial (low risk of bias) found cough, cough-related QoL and respiratory-related QoL were significantly improved with thalidomide compared with placebo. Adverse events were experienced with thalidomide. Caution is required given the small sample size. *Sildenafil:* One RCT (unclear risk of bias) found no significant difference between sildenalfil and placebo in the proportion with a 20% improvement on 6MWT (primary outcome). Dyspnoea may be improved (depending on the measure used and test conditions). QoL was better in those treated with sildenafil when measured using the SGRQ, but not when using the SF-36 or the EQ-5D. Adverse events were similar between groups. *Disease management programme:* One pilot RCT (unclear risk of bias) found no significant differences in dyspnoea compared to usual care. QoL appeared to be adversely affected on measures of physical health but not on measures of mental health. The study was unlikely to be sufficiently powered. *PR:* One RCT (unclear risk of bias) and one CCT (high risk of bias) provided uncertain results as to the effects of these types of intervention, and there were baseline differences between groups on many key outcomes.
Review conclusions	Few interventions have any statistically significant effect on IPF and a lack of studies on palliative care approaches was identified. Research is required into the effects of symptom control interventions, in particular pulmonary rehabilitation and thalidomide.

Author, year, EN#	Dowman et al 2014[3]
Study population	People with ILD of any origin (includes sarcoidosis)
Intervention(s)	Pulmonary rehabilitation (any prescribed exercise training, with or without education, supervised or unsupervised, combined with another intervention permitted)
Included studies, N Reference details	9 RCTs (6 published as abstracts only), up to 5 included in meta-analysis. (Note: RCTs with sarcoidosis not in meta-analyses) Baradzina 2005 (abstract) Holland 2008 Jackson 2014 (ahead of print) Mejia 2000 (abstract) Menon 2011 (abstract) Nishiyama 2008 Perez Bogerd 2011 (abstract) Vainshelboim 2013 (abstract) Wewel 2005 (abstract)
Results (relevant outcomes)	In 8 trials (n=365) PR significantly improved functional exercise capacity immediately following the programme, no significant change on 6MWD in the other 1 study. Pooled analysis of change in 6MWD from 5 RCTs (168 participants) was MD 44.34 metres (95%CI 26.04, 66.64), I^2 14%. favouring PR. GRADE[a]: moderate quality. No significant effect of PR evident on 6MWD in 2 studies reporting longer-term follow-up (3 and 6 months respectively). In 5 trials (n=281) 3 reported reduced dyspnoea following PR; 2 reported no change in dyspnoea. Pooled analysis of 3 studies (113 participants) SMD for change in dyspnoea was -0.66 (95% CI -1.05, -0.28), I^2 49%, in favour of PR. GRADE[a]: low quality. No significant effect of PR evident on dyspnoea in 1 study reporting a 6-month follow-up. In 8 trials measured HRQoL and 3 found significant differences immediately following PR (2 others non-significant improvements, remaining 3 unclear). Pooled analysis of 3 studies (106 participants) SMD 0.59 (95% CI 0.20, 0.98) I^2 0%. in favour of PR. GRADE[a]: low quality. No significant effect of PR evident on HRQoL in 2 studies reporting longer-term follow-up (3 and 6 months respectively). Subgroup analyses by subtype of ILD reported, not extracted. No adverse events in two studies that reported it.
Review conclusions	PR seems to be safe for people with ILD. Improvements in functional exercise capacity, dyspnoea and quality of life are seen immediately following pulmonary rehabilitation, with benefits also evident in IPF. Because of inadequate reporting of methods and small numbers of included participants, the quality of evidence was low to moderate. Little evidence was available regarding longer-term effects of pulmonary rehabilitation.

Appendix B: Search strategy

Medline search

Ovid MEDLINE(R) ALL 1946 to January 14, 2019
1. idiopathic pulmonary fibrosis.tw.
2. interstitial lung disease*.tw.
3. non-specific interstitial pneumonia*.tw.
4. idiopathic interstitial pneumonia*.tw.
5. cryptogenic organi* pneumonia*.tw.
6. (IPF or ILD or IIP or NSIP).m_titl.
7. Idiopathic Pulmonary Fibrosis/dt, pc, rh, su [Drug Therapy, Prevention & Control, Rehabilitation, Surgery]

8. Lung Diseases, Interstitial/dt, pc, rh, su [Drug Therapy, Prevention & Control, Rehabilitation, Surgery]
9. Idiopathic Interstitial Pneumonias/dt, pc, th [Drug Therapy, Prevention & Control, Therapy]
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. (comment or letter or editorial).pt.
12. 10 not 11
13. limit 12 to yr="2011 -Current"
14. animals/
15. Humans/
16. 14 not (14 and 15)
17. 13 not 16

Ovid Embase 1974 to 2019 January 14
1. *interstitial lung disease/dm, dr, dt, rh, su, th [Disease Management, Drug Resistance, Drug Therapy, Rehabilitation, Surgery, Therapy]
2. *interstitial pneumonia/dt, rh [Drug Therapy, Rehabilitation]
3. idiopathic pulmonary fibrosis.tw.
4. interstitial lung disease*.tw.
5. non-specific interstitial pneumonia*.tw.
6. idiopathic interstitial pneumonia*.tw.
7. cryptogenic organi* pneumonia*.tw.
8. (IPF or ILD or IIP or NSIP).m_titl.
9. (letter or editorial).pt.
10. conference.pt.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
12. 11 not 9
13. limit 12 to yr="2011 -Current"
14. 10 and 13
15. 13 not 14

Web of Science Core Collection
TOPIC: (idiopathic pulmonary fibrosis) OR TOPIC: (interstitial lung disease*) OR TOPIC: (idiopathic interstitial pneumonia*) OR TOPIC: (non-specific interstitial pneumonia*)
Refined by: DOCUMENT TYPES: (ARTICLE OR REVIEW OR MEETING ABSTRACT
Timespan: 2011-2019. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.

Cochrane Library: Cochrane Database of Systematic Reviews (Issue 1 of 12 January 2019) and Cochrane Central Register of Controlled Trials (Issue 1 of 12, January 2019)
Search: 'idiopathic pulmonary fibrosis OR interstitial lung disease* OR idiopathic interstitial pneumonia* OR non-specific interstitial pneumonia* or cryptogenic organ* pneumonia OR IPF or ILD or IIP or NSIP in Title, Abstract, Keywords, Publication Year from 2011 to 2019.

CRD databases https://www.crd.york.ac.uk/CRDWeb/
Search: 'idiopathic pulmonary fibrosis OR interstitial lung disease* OR idiopathic interstitial pneumonia* OR non-specific interstitial pneumonia* or cryptogenic organ* pneumonia OR IPF or ILD or IIP or NSIP: 2011 to 2019.

Ongoing studies

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/
- WHO International Clinical Trials Registry Platform (ICTRP) http://www.who.int/ictrp/en/
- UK Clinical Trials Gateway. https://www.ukctg.nihr.ac.uk
- PROSPERO – Ongoing reviews

Searched using keywords:
idiopathic pulmonary fibrosis OR interstitial lung disease OR non-specific interstitial pneumonia OR idiopathic interstitial pneumonia* OR cryptogenic organizing pneumonia

Auto-alerts
Set up to run weekly in Medline and Embase from Feb 2nd to November 2017. Searches were then updated from November 2017 to January 2019.

1. Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel AS, Koffman J, Riley J. Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature. *Thorax* 2013: 68(9): 867-879.
2. Loveman E, Copley VR, Colquitt J, Scott DA, Clegg A, Jones J, O'Reilly KM, Singh S, Bausewein C, Wells A. The clinical effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: a systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)* 2015: 19(20): i-xxiv, 1-336.
3. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database of Systematic Reviews* 2014(10): CD006322.

Suppl 2 Excluded but potentially relevant studies

Table 1 Reasons for exclusion

Study	Reason for exclusion
Abe 2015[1]	Not palliative intent/symptom control
Adams 2016[2]	Study design
Alhamad 2015[3]	Not palliative intent/symptom control
Anon 2015[4]	Not palliative intent/symptom control
Anonymous 2016[5]	Not palliative intent/symptom control
Arizono 2015[6]	Outcomes
Assayag 2015[7]	Study design
Azuma 2011[8]	Not palliative intent/symptom control
Azuma 2016[9]	Not palliative intent/symptom control
Behr 2014[10]	Not palliative intent/symptom control
Behr 2015[11]	Not palliative intent/symptom control
Behr 2015[12]	Not palliative intent/symptom control
Behr 2016[13]	Not palliative intent/symptom control
Blanco 2011[14]	Outcomes
Bogerd 2011[15]	In previous reviews
Bonella 2016[16]	Study design
Brown 2012[17]	Intervention
Brunnermer 2016[18]	Not palliative intent/symptom control
Cameli 2014[19]	Intervention
Cao 2015[20]	Study design
Chambers 2014[21]	Not palliative intent/symptom control
Chaudhuri 2014[22]	Not palliative intent/symptom control
Costabel 2011[23]	Not palliative intent/symptom control
Costabel 2011[24]	Not palliative intent/symptom control
Costabel 2014[25]	Not palliative intent/symptom control
Costabel 2016[26]	Not palliative intent/symptom control
Couluris 2012[27]	Not palliative intent/symptom control
Crestani 2015 [28]	Not palliative intent/symptom control
Currow 2011[29]	Data for fibrotic ILD not reported [a]
Da Fontoura 2018[30]	Study design
Dale 2014[31]	Participants
Diaz 2012[32]	Not palliative intent/symptom control
Dowman 2016[33]	Study design
Dreher 2015[34]	Study design
Ekstrom 2016[35]	Not palliative intent/symptom control
Enomoto 2016[36]	Not palliative intent/symptom control
Florian 2013[37]	Mixed lung disease[a]
Gaunaurd 2013[38]	In previous reviews
Gaunaurd 2014[39]	In previous reviews
Gomez 2012[40]	In previous reviews
Gomez 2013[41]	In previous reviews

Gomez 2014[42]	In previous reviews
Greening 2014[43]	Mixed lung disease[a]
Han 2013[44]	Study design
Hanada 2016[45]	Data for fibrotic ILD not reported [a]
Heinzelmann 2015[46]	Outcomes
Higginson 2014[47]	Data for fibrotic ILD not reported [a]
Hirani 2017[48]	Outcomes
Holland 2014[49]	Study design
Homma 2012[50]	Not palliative intent/symptom control
Hosein 2016[51]	Not palliative intent/symptom control
Huang 2015[52]	Not palliative intent/symptom control
Huang 2015[53]	Not palliative intent/symptom control
Huppmann 2013[54]	Mixed lung disease[a]
IPFCRN 2012[55]	Not palliative intent/symptom control
IPFCRN 2014[56]	Not palliative intent/symptom control
Jager-Becker 2016[57]	Not palliative intent/symptom control
Jastrzebski 2013[58]	Mixed lung disease[a]
Kalluri 2016[59]	Study design
Kalluri 2017[60]	Study design
Kamio 2014 [61]	Outcomes
Kataoka 2015[62]	Intervention
Kawamura 2014[63]	Intervention / outcomes
Kaymaz 2013[64]	Study design
King 2014[65]	Intervention
Kolb 2016[66]	Study design
Kramer 2013[67]	In previous reviews
Kramer 2014[68]	In previous reviews
Lavender 2011[69]	Study design
Maher 2017[70]	Outcomes
Marti 2013[71]	Study design
Mermigkis 2011[72]	Intervention
Mermigkis 2013 [73]	Participants
Mermigkis 2014[74]	Participants
Migita 2014[75]	Study design
Mohamed 2014[76]	Mixed lung disease[a]
Nishiyama 2013[77]	Study design
Nolan 2017[78]	Study design
Noble 2011[79]	Not palliative intent/symptom control
Ogura 2015[80]	Not palliative intent/symptom control
Okuda 2016[81]	Outcomes
Oltmanns 2014[82]	Study design
Pan 2016[83]	Not palliative intent/symptom control
Polo?ski 2017[84]	Not palliative intent/symptom control
Raghu 2012[85]	Not palliative intent/symptom control

Raghu 2012[86]	Not palliative intent/symptom control
Raghu 2013[87]	Not palliative intent/symptom control
Raghu 2013[88]	Not palliative intent/symptom control
Raghu 2015[89]	Not palliative intent/symptom control
Raghu 2016 [90]	Not palliative intent/symptom control
Raghu 2016 [91]	Not palliative intent/symptom control
Raghu 2017 [92]	Not palliative intent/symptom control
Restivo 2017[93]	Participants
Richeldi 2011[94]	Not palliative intent/symptom control
Richeldi 2014[95]	Not palliative intent/symptom control
Richeldi 2014[96]	Not palliative intent/symptom control
Richeldi 2014[97]	Not palliative intent/symptom control
Richeldi 2015[98]	Not palliative intent/symptom control
Richeldi 2016 [99]	Not palliative intent/symptom control
Ryerson 2016[100]	Not palliative intent/symptom control
Saini 2011[101]	Study design
Sakamoto 2015[102]	Not palliative intent/symptom control
Salem 2014[103]	Not palliative intent/symptom control
Saunders 2017[104]	Intervention
Scalori 2014[105]	Not palliative intent/symptom control
Schaeffer 2015[106]	Study design
Sgalla 2015[107, 108]	Data for fibrotic ILD not reported [a]
Sharp 2015 [109]	Study design
Sharp 2016[110]	Study design
Shimizu 2014[111]	Not palliative intent/symptom control
Shulgina 2013[112]	Not palliative intent/symptom control
Skovhus Prior 2015[113]	Outcomes
Soares 2011 [114]	Not palliative intent/symptom control
Suraj 2016 [115]	Not palliative intent/symptom control
Taguchi 2015[116]	Not palliative intent/symptom control
Taniguchi 2014 [117]	Not palliative intent/symptom control
Taniguchi 2016[118]	Not palliative intent/symptom control
Tonelli 2017[119]	Data for fibrotic ILD not reported [a]
Triantafillidou 2013[120]	Intervention
Troy 2014[121]	Study design
Troy 2015[122]	Outcomes
Tzouvelekis 2013 [123]	Not palliative intent/symptom control
Vainshelboim 2015[124]	Outcomes
Vieira2011[125]	Study design
Vitale 2014[126]	Not palliative intent/symptom control
Watanabe 2011[127]	Unable to retrieve (Japanese)[a]
Wilson 2014[128]	Not palliative intent/symptom control

[a]Attempted to contact authors

Table 2 Abstracts published 2015 onwards with insufficient information for inclusion (attempted to contact authors)

Parisien-La Salle 2019[129]
Sciriha 2019[130]
Naz 2018[131]
Ochman 2018 [132]
Perez Bogerd 2018[133]
Camcioglu 2017[134]
Koczulla 2017[135]
Kondoh 2017[136]
Lam 2017[137]
Matsuda 2017[138]
Aghbari 2016[139]
Koulopoulou 2016[140, 141]
Nykvist 2016[142]
Stanley 2016[143]
Stessel 2015[144]

Excluded abstracts published prior to 2015

1. Arizono, S., et al., *Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis: Comparison with COPD.* European Respiratory Journal. Conference: European Respiratory Society Annual Congress, 2013. **42**(no pagination).
2. Barbier, V., et al., *Survival rates after a rehabilitation program in patients with interstitial lung disease.* European Respiratory Journal. Conference: European Respiratory Society Annual Congress, 2014. **44**(no pagination).
3. Cottin, V., et al., *Treatment of severe pulmonary hypertension in patients with interstitial lung disease: Results in 72 patients from the "HYPID" prospective study.* European Respiratory Journal. Conference: European Respiratory Society Annual Congress, 2013. **42**(no pagination).
4. Dierich, M.G., et al., *Benefit of pulmonary rehabilitation in candidates for lung transplantation.* European Respiratory Journal. Conference: European Respiratory Society Annual Congress, 2011. **38**(no pagination).
5. Fell, C.D., et al., *Yoga for idiopathic pulmonary fibrosis: A pilot study.* American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS, 2011. **183**(1 Meeting Abstracts).
6. Hussain, M.J., et al., *Pulmonary rehabilitation outcomes in chronic obstructive pulmonary disease (COPD) vs matched patients with interstitial lung disease (ILD).* Thorax, 2012. **67**: p. A53-A54.
7. Jackson, R.M., et al., *Exercise limitations and rehabilitation of IPF patients.* American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS, 2014. **189**(no pagination).
8. Kozu, R., et al., *Effect of disability on response to pulmonary rehabilitation (PR) in individuals with idiopathic pulmonary fibrosis (IPF).* Respirology, 2011. **16**: p. 20.
9. Lardner, R., et al., *The benefits of pulmonary rehabilitation (PR) in interstitial lung disease (ILD): Observations from oxfordshire's mixed respiratory disease, community based PR programme.* Thorax. 2014;69:A132-A3.
10. Li, H., et al., *The efficacy and safety of chinese herb on the treatment of idiopathic pulmonary fibrosis.* Chest. Conference: CHEST, 2012. **142**(4 SUPPL. 1).
11. Mejia, R., et al., *Effects of exercise training on 'quality of life' in patients withinterstitial lung diseases (abstract).* European RespiratoryJournal. 2000;16(Suppl 31):330s.
12. Menon, B., V. Bansal, and B. Prajapat, *Effect of pulmonary rehabilitation on systemic inflammatory markers, muscle cross section area and functional parameters in interstitial lung disease.* European Respiratory Journal. Conference: European Respiratory Society Annual Congress, 2012. **40**(no pagination).

13. Menon, B., et al., *Effect of pulmonary rehabilitation on gas exchange, muscle cross section area and functional parameters in interstitial lung disease [Abstract]*. European Respiratory Society Annual Congress, Amsterdam, The Netherlands, September 24-28 [Internet]. 2011; 38(55):[878s [P4798] p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/609/CN-00833609/frame.html.
14. Mira-Avendano, I.C., et al., *Administration of oral sildenafil does not affect diffusion capacity measurements in patients with diffuse parenchymal lung disease and pulmonary hypertension.* American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS, 2013. **187**(no pagination).
15. Mishima, T., et al., *Effects of in-patient pulmonary rehabilitation for advanced idiopathic pulmonary fibrosis.* Respirology, 2013. **18**: p. 136.
16. Mishima, T., et al., *Benefits of pulmonary rehabilitation and predictor of changes in exercise capacity for idiopathic pulmonary fibrosis.* European Respiratory Journal. Conference: European Respiratory Society Annual Congress, 2014. **44**(no pagination).
17. Nakazawa, A., et al., *Comparison of efficacy of respiratory rehabilitation in patients with COPD and interstitial lung disease.* European Respiratory Journal. Conference: European Respiratory Society Annual Congress, 2011. **38**(no pagination).
18. Peasey, M.M., et al., *Pulmonary rehabilitation in interstitial lung disease patients: Effects on maximum exercise capacity, anxiety and depression.* Thorax, 2012. **67**: p. A106.
19. Perez Bogerd, S., et al., *Preliminary results of pulmonary rehabilitation in interstitial lung diseases: a randomised controlled trial B32220095560 [Abstract]*. European Respiratory Society Annual Congress. 2011;38(55):259s.
20. Tomioka, H., et al., *Comparison of the effect of inpatient pulmonary rehabilitation between interstitial lung disease (ILD) and chronic obstructive pulmonary diseases (COPD).* American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2011;183(1 Meeting Abstracts).
21. Wewel, A., et al., *Home-based walking training in patients with interstitial lung diseases (abstract).* European Respiratory Journal. 2005;26:528S.
22. Woolstenhulme, J.G., et al., *Effects of a 10-week Aerobic Exercise Program on Cardiorespiratory Function in Patients with Interstitial Lung Disease.* Medicine and Science in Sports and Exercise, 2012. **44**: p. 601-601.
23. Woolstenhulme, J.G., et al., *Aerobic exercise attenuates fatigability and fatigue in patients with interstitial lung disease.* American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2013;187(no pagination).
24. Yilmaz, A., et al., *The effectiveness of exercise-based pulmonary rehabilitation in patients with pulmonary disease, Pulmoner rehabilitasyon hastalarinda aerobik egzersiz temelli rehabilitasyonun etkinliti. [Turkish, English]*. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi, 2011. **57**: p. 273.
25. Zatloukal, J., et al., *Effect of the 6-week rehabilitation programme in patients with ILD.* European Respiratory Journal. Conference: European Respiratory Society Annual Congress, 2013. **42**(no pagination).

References

1. Abe M, Tsushima K, Matsumura T, Ishiwata T, Ichimura Y, Ikari J, Terada J, Tada Y, Sakao S, Tanabe N, Tatsumi K. Efficacy of thrombomodulin for acute exacerbation of idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia: a nonrandomized prospective study. *Drug design, development & therapy* 2015: 9: 5755-5762.
2. Adams TN, Eiswirth C, Newton CA, Battaile JT. Pirfenidone for Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory & Critical Care Medicine* 2016: 194(3): 374-376.
3. Alhamad EH. Pirfenidone treatment in idiopathic pulmonary fibrosis: A Saudi experience. *Annals of Thoracic Medicine* 2015: 10(1): 38-43.
4. The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary fibrosis with the Addition of Co-trimoxazole (EME-TIPAC) (Project record). Health Technology Assessment Database. Health Technology Assessment, 2015.
5. Anonymous. Pulmonary rehabilitation in idiopathic pulmonary fibrosis. [Japanese]. *Therapeutic Research* 2016: 37(6): 539.
6. Arizono S, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K. Benefits of supplemental oxygen on exercise capacity in IPF patients with exercise-induced hypoxemia. European Respiratory Journal, 2015.
7. Assayag D, Vittinghoff E, Ryerson CJ, Cocconcelli E, Tonelli R, Hu X, Elicker BM, Golden JA, Jones KD, King TE, Jr., Koth LL, Lee JS, Ley B, Shum AK, Wolters PJ, Ryu JH, Collard HR. The effect of bronchodilators on forced vital capacity measurement in patients with idiopathic pulmonary fibrosis. *Respiratory Medicine* 2015: 109(8): 1058-1062.
8. Azuma A, Taguchi Y, Ogura T, Ebina M, Taniguchi H, Kondoh Y, Suga M, Takahashi H, Nakata K, Sato A, Kudoh S, Nukiwa T, Pirfenidone Clinical Study Group in J. Exploratory analysis of a phase III trial of pirfenidone identifies a subpopulation of patients with idiopathic pulmonary fibrosis as benefiting from treatment. *Respiratory Research* 2011: 12: 143.
9. Azuma A, Taniguchi H, Inoue Y, Kondoh Y, Ogura T, Homma S, Fujimoto T, Sakamoto W, Sugiyama Y, Nukiwa T. Nintedanib in Japanese patients with idiopathic pulmonary fibrosis: A subgroup analysis of the INPULSIS randomized trials. *Respirology* 2016: 20.
10. Behr J, Bendstrup E, Crestani B, G¸nther A, Olschewski H, Skoeld M. A Phase 2, double-blind, placebo-controlled study of N?acetylcysteine in combination with pirfenidone in patients with idiopathic pulmonary fibrosis [Abstract]. European Respiratory Journal, 2014; p. P3786.
11. Behr J, Bendstrup E, Crestani B, Gnther A, Olschewski H, Skld M. Safety and tolerability of N-acetylcysteine (NAC) with pirfenidone in idiopathic pulmonary fibrosis (IPF): PANORAMA. European Respiratory Journal, 2015.
12. Behr J, Bendstrup E, Crestani B, Gunther A, Olschewski H, Skold M. Pirfenidone and N-acetylcysteine (NAC) for the treatment of Idiopathic Pulmonary Fibrosis (IPF): Exploratory efficacy results from the PANORAMA study. Chest, 2015.
13. Behr J, Bendstrup E, Crestani B, Gunther A, Olschewski H, Skold CM, Wells A, Wuyts W, Koschel D, Kreuter M, Wallaert B, Lin CY, Beck J, Albera C. Safety and tolerability of acetylcysteine and pirfenidone combination therapy in idiopathic pulmonary fibrosis: a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet Respiratory Medicine* 2016: 4(6): 445-453.
14. Blanco I, Ribas J, Xaubet A, Gomez FP, Roca J, Rodriguez-Roisin R, Barbera JA. Effects of inhaled nitric oxide at rest and during exercise in idiopathic pulmonary fibrosis. *Journal of Applied Physiology* 2011: 110(3): 638-645.
15. Bogerd SP, Wuyts W, Barbier V, Langer D, Burtin C, Van Remoortel H, Decramer M, Troosters T, Janssens W. Preliminary results of pulmonary rehabilitation in interstitial lung diseases: A randomised controlled trial B32220095560. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2011: 38(no pagination).
16. Bonella F, Kreuter M, Hagmeyer L, Neurohr C, Keller C, Kohlhaeufl MJ, Muller-Quernheim J, Milger K, Prasse A, German Nintedanib Compassionate Use C. Insights from the German

Compassionate Use Program of Nintedanib for the Treatment of Idiopathic Pulmonary Fibrosis. *Respiration* 2016: 92(2): 98-106.
17. Brown KK, Richeldi L, Costabel U, Flaherty KR, Kim DS, Noble PW. Treatment Of IPF With The Tyrosine Kinase Inhibitor BIBF 1120: Patient-Reported Outcomes In The TOMORROW Trial [Abstract]. American journal of respiratory and critical care medicine, 2012; p. A3634.
18. Brunnemer E, Ehlers-Tenenbaum S, Heussel CP, Warth A, Herth F, Kreuter M. Real life experience with nintedanib in patients with idiopathic pulmonary fibrosis. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
19. Cameli P, Bargagli E, Refini RM, Pieroni MG, Bennett D, Rottoli P. Exhaled nitric oxide in interstitial lung diseases. *Respiratory Physiology & Neurobiology* 2014: 197: 46-52.
20. Cao M, Wamboldt FS, Brown KK, Hickman J, Olson AL, Solomon JJ, Swigris JJ. Supplemental oxygen users with pulmonary fibrosis perceive greater dyspnea than oxygen non-users. *Multidisciplinary Respiratory Medicine* 2015: 10: 37.
21. Chambers DC, Enever D, Ilic N, Sparks L, Whitelaw K, Ayres J, Yerkovich ST, Khalil D, Atkinson KM, Hopkins PM. A phase 1b study of placenta-derived mesenchymal stromal cells in patients with idiopathic pulmonary fibrosis. *Respirology* 2014: 19(7): 1013-1018.
22. Chaudhuri N, Duck A, Frank R, Holme J, Leonard C. Real world experiences: pirfenidone is well tolerated in patients with idiopathic pulmonary fibrosis. *Respiratory Medicine* 2014: 108(1): 224-226.
23. Costabel U, Albera C, Cohen A, Bradford W, King T, Noble P. The long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis (IPF): Interim data from the RECAP extension study [Abstract]. European Respiratory Society Annual Congress, Amsterdam, The Netherlands, September 24-28, 2011; p. 3s [174].
24. Costabel U, Richeldi L, Selman M, Kim DS, Brown KK, Flaherty KR. Efficacy of BIBF 1120 in patients with IPF is dose-dependent: Results from the TOMORROW trial [Abstract]. European Respiratory Society Annual Congress, Amsterdam, The Netherlands, September 24-28, 2011; p. 2s [172].
25. Costabel U, Albera C, Bradford WZ, Hormel P, King TE, Jr., Noble PW, Sahn SA, Valeyre D, du Bois RM. Analysis of lung function and survival in RECAP: An open-label extension study of pirfenidone in patients with idiopathic pulmonary fibrosis. *Sarcoidosis Vasculitis & Diffuse Lung Diseases* 2014: 31(3): 198-205.
26. Costabel U, Inoue Y, Richeldi L, Collard HR, Tschoepe I, Stowasser S, Azuma A. Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis across Prespecified Subgroups in INPULSIS. *American Journal of Respiratory & Critical Care Medicine* 2016: 193(2): 178-185.
27. Couluris M, Kinder BW, Xu P, Gross-King M, Krischer J, Panos RJ. Treatment of idiopathic pulmonary fibrosis with losartan: a pilot project. *Lung* 2012: 190(5): 523-527.
28. Crestani B, Ogura T, Pelling K, Quaresma M, Coeck C, Kaye M. Safety and tolerability of nintedanib in patients with IPF: Interim analysis from an open-label extension of the inpulsis trials (inpulsis-on). American Journal of Respiratory and Critical Care Medicine, 2015; p. A1020.
29. Currow DC, McDonald C, Oaten S, Kenny B, Allcroft P, Frith P, Briffa M, Johnson MJ, Abernethy AP. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *Journal of Pain and Symptom Management* 2011: 42(3): 388-399.
30. da Fontoura FF, Berton DC, Watte G, Florian J, Schio SM, Camargo JdJP, Teixeira PJZ, Moreira JdS. Pulmonary Rehabilitation in Patients With Advanced Idiopathic Pulmonary Fibrosis Referred for Lung Transplantation. *Journal of cardiopulmonary rehabilitation and prevention* 2018: 38(2): 131-134.
31. Dale MT, McKeough ZJ, Munoz PA, Corte P, Bye PTP, Alison JA. Exercise training for asbestos-related and other dust-related respiratory diseases: a randomised controlled trial. *Bmc Pulmonary Medicine* 2014: 14.

32. Diaz KT, Skaria S, Harris K, Solomita M, Lau S, Bauer K, Smaldone GC, Condos R. Delivery and safety of inhaled interferon-gamma in idiopathic pulmonary fibrosis. *Journal of aerosol medicine & pulmonary drug delivery* 2012: 25(2): 79-87.
33. Dowman LM, McDonald CF, Bozinovski S, Vlahos R, Gillies R, Pouniotis D, Hill CJ, Goh NS, Holland AE. Greater endurance capacity and improved dyspnoea with acute oxygen supplementation in idiopathic pulmonary fibrosis patients without resting hypoxaemia. *Respirology* 2017: 22.
34. Dreher M, Ekkernkamp E, Schmoor C, Schoenheit-Kenn U, Winterkamp S, Kenn K. Pulmonary rehabilitation and noninvasive ventilation in patients with hypercapnic interstitial lung disease. *Respiration* 2015: 89(3): 208-213.
35. Ekstrom M, Bornefalk-Hermansson A. Cardiovascular and antacid treatment and mortality in oxygen-dependent pulmonary fibrosis: A population-based longitudinal study. *Respirology* 2016: 21(4): 705-711.
36. Enomoto N, Chida K, Suda T, Kaida Y, Taniguchi M, Azuma A, Hayashi H, Ogura T, Kitamura H, Yamaguchi O, Ando M, Sato A, Kudo S. An exploratory trial of intravenous immunoglobulin therapy for idiopathic pulmonary fibrosis: a preliminary multicenter report. *The clinical respiratory journal* 2016: 10(6): 746-755.
37. Florian J, Rubin A, Mattiello R, Fontoura FF, Camargo Jde J, Teixeira PJ. Impact of pulmonary rehabilitation on quality of life and functional capacity in patients on waiting lists for lung transplantation. *Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia* 2013: 39(3): 349-356.
38. Gaunaurd IA, Gomez-Marin O, Ramos C, Cardenas D, Cahalin L, Cohen M, Jackson RM. Effects of a pulmonary rehabilitation on exercise capacity and functional mobility for patient with IPF. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2013: 187(no pagination).
39. Gaunaurd IA, Gomez-Marin O, Ramos C, Cardenas D, Cahalin L, Cohen M, Jackson RM. Effects of a pulmonary rehabilitation on exercise capacity and functional mobility for patient with IPF. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2014: 189(no pagination).
40. Gomez O, Ramos CF, Cardenas D, Gaunaurd I, Eustis N, Cohen M, Jackson RM. Exercise training during pulmonary rehabilitation increases activity levels of IPF patients. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2012: 185(no pagination).
41. 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, 2013.
42. 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: 189(no pagination).
43. Greening NJ, Williams JE, Hussain SF, Harvey-Dunstan TC, Bankart MJ, Chaplin EJ, Vincent EE, Chimera R, Morgan MD, Singh SJ, Steiner MC. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. *BMJ* 2014: 349: g4315.
44. Han MK, Bach DS, Hagan PG, Yow E, Flaherty KR, Toews GB, Anstrom KJ, Martinez FJ, Investigators IP. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. *Chest* 2013: 143(6): 1699-1708.
45. Hanada M, Sakamoto N, Ishimatsu Y, Kakugawa T, Obase Y, Kozu R, Senjyu H, Izumikawa K, Mukae H, Kohno S. Effect of long-term treatment with corticosteroids on skeletal muscle strength, functional exercise capacity and health status in patients with interstitial lung disease. *Respirology* 2016: 21(6): 1088-1093.

46. Heinzelmann I, Gloeckl R, Matthaei M, Damisch T, Sczepanski B, Jerrentrup A. Benefits of a reservoir nasal cannula (oxymizer) versus a conventional nasal cannula during exercise in hypoxemic patients with interstitial lung diseases. American Journal of Respiratory and Critical Care Medicine, 2015; p. A5302.
47. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, McCrone P, Booth S, Jolley CJ, Moxham J. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med* 2014: 2(12): 979-987.
48. Hirani N, Mackinnon A, Nicol L, Walker J, Ford P, Schambye H, Pederson A, Nilsson U, Leffler H, Thomas T, Francombe D, Simpson J, Gibbons M, Maher TM. Td139, A Novel Inhaled Galectin-3 Inhibitor For The Treatment Of Idiopathic Pulmonary Fibrosis (ipf). Results From The First In (ipf) Patients Study. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
49. Holland A, Goh N, Hazard A, Symons K, McDonald C, Westal l G. Effects of the evergo portable oxygen concentrator on exertional desaturation in people with interstitial lung disease [Abstract]. Respirology (Carlton, Vic), 2014; p. 91 [tp 106].
50. Homma S, Azuma A, Taniguchi H, Ogura T, Mochiduki Y, Sugiyama Y, Nakata K, Yoshimura K, Takeuchi M, Kudoh S, Japan NACCSG. Efficacy of inhaled N-acetylcysteine monotherapy in patients with early stage idiopathic pulmonary fibrosis. *Respirology* 2012: 17(3): 467-477.
51. Hosein K, Le J, Mura M. Assessing the Therapeutic Response to Pirfenidone in Idiopathic Pulmonary Fibrosis: Can We Do Better than with Forced Vital Capacity Alone? *Lung* 2016: 17.
52. Huang H, Dai HP, Kang J, Chen BY, Sun TY, Xu ZJ. Double-Blind Randomized Trial of Pirfenidone in Chinese Idiopathic Pulmonary Fibrosis Patients. *Medicine* 2015: 94(42): e1600.
53. Huang H, Xu Z, Kang J, Dai H, Chen B, Sun T. Double-blind, placebo-controlled, randomized trial of pirfenidone in Chinese idiopathic pulmonary fibrosis patients. American Journal of Respiratory and Critical Care Medicine, 2015; p. A4412.
54. Huppmann P, Sczepanski B, Boensch M, Winterkamp S, Schonheit-Kenn U, Neurohr C, Behr J, Kenn K. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. *European Respiratory Journal* 2013: 42(2): 444-453.
55. Idiopathic Pulmonary Fibrosis Clinical Research N, Raghu G, Anstrom KJ, King TE, Jr., Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *New England Journal of Medicine* 2012: 366(21): 1968-1977.
56. Idiopathic Pulmonary Fibrosis Clinical Research N, Martinez FJ, de Andrade JA, Anstrom KJ, King TE, Jr., Raghu G. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. *New England Journal of Medicine* 2014: 370(22): 2093-2101.
57. Jager-Becker D, Stiefelhagen P. Idiopathic pulmonary fibrosis: Long-term treatment slows down progression. *MMW-Fortschritte der Medizin* 2016: 158(3): 68.
58. Jastrzebski D, Ochman M, Ziora D, Labus L, Kowalski K, Wyrwol J, Lutogniewska W, Maksymiak M, Ksiazek B, Magner A, Bartoszewicz A, Kubicki P, Hydzik G, Zebrowska A, Kozielski J. Pulmonary rehabilitation in patients referred for lung transplantation. *Advances in Experimental Medicine & Biology* 2013: 755: 19-25.
59. Kalluri M, Claveria F, Haggag M, Richman-Eisenstat J. Early Integrated Palliative Care in a Multidisciplinary Interstitial Lung Disease (ILD) Collaborative Reduces Hospitalizations for Idiopathic Pulmonary Fibrosis (IPF). *Chest* 2016: 150(4): 472A-472A.
60. Kalluri M, Richman-Eisenstat J. Early and Integrated Palliative Care to Achieve a Home Death in Idiopathic Pulmonary Fibrosis. *Journal of Pain & Symptom Management* 2017: 53(6): 1111-1115.
61. Kamio K, Azuma A, Ohta K, Sugiyama Y, Nukiwa T, Kudoh S, Mizushima T. Double-blind controlled trial of lecithinized superoxide dismutase in patients with idiopathic interstitial pneumonia - short term evaluation of safety and tolerability. *BMC Pulmonary Medicine* 2014: 14: 86.
62. Kataoka K, Taniguchi H, Kondoh Y, Nishiyama O, Kimura T, Matsuda T, Yokoyama T, Sakamoto K, Ando M. Recombinant Human Thrombomodulin in Acute Exacerbation of Idiopathic Pulmonary Fibrosis. *Chest* 2015: 148(2): 436-443.

63. Kawamura K, Ichikado K, Suga M, Yoshioka M. Efficacy of azithromycin for treatment of acute exacerbation of chronic fibrosing interstitial pneumonia: a prospective, open-label study with historical controls. *Respiration* 2014: 87(6): 478-484.
64. Kaymaz D, Ergun P, Candemir I, Utku E, Demir N, Sengul F, Egesel N, Demir P. Pulmonary rehabilitation in interstitial lung diseases. *Tuberkuloz ve Toraks* 2013: 61(4): 295-302.
65. King TE, Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW, Group AS. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis.[Erratum appears in N Engl J Med. 2014 Sep 18;371(12):1172]. *New England Journal of Medicine* 2014: 370(22): 2083-2092.
66. Kolb M, Richeldi L, Behr J, Maher TM, Tang W, Stowasser S, Hallmann C, du Bois RM. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. *Thorax* 2016: 26.
67. Kramer M, Vainshelboim B, Oliveira J, Yohoshua L, Wais I, Rusanov V, Fruchter O. Pulmonary rehabilitation improves exercise capacity and function in patients with idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine, 2013.
68. Kramer M, Vainshelboim B, Oliveira J, Yohoshua L, Wais I, Rusanov V, Fruchter O. Pulmonary rehabilitation improves exercise capacity and function in patients with idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2014: 189(no pagination).
69. Lavender M. Sildenafil does not improve 6 min walk distance in advanced idiopathic pulmonary fibrosis. *Thorax* 2011: 66(3): 239.
70. Maher TM, Biddiscombe M, Fahy WA, Lukey P, Marshall RP, Meah S, Oballa E, Simpson JK, Yang S, Usmani O. The Topical Study Of Inhaled Drug (salbutamol) Delivery In Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
71. Marti S, Pajares V, Morante F, Ramon MA, Lara J, Ferrer J, Guell MR. Are oxygen-conserving devices effective for correcting exercise hypoxemia? *Respiratory Care* 2013: 58(10): 1606-1613.
72. Mermigkis C, Mermigkis D, Varouchakis G, Schiza S. CPAP treatment in patients with idiopathic pulmonary fibrosis and obstructive sleep apnea-therapeutic difficulties and dilemmas. *Sleep and Breathing* 2011: 1-3.
73. Mermigkis C, Bouloukaki I, Antoniou KM, Mermigkis D, Psathakis K, Giannarakis I, Varouchakis G, Siafakas N, Schiza SE. CPAP therapy in patients with idiopathic pulmonary fibrosis and obstructive sleep apnea: does it offer a better quality of life and sleep? *Sleep & Breathing* 2013: 17(4): 1137-1143.
74. Mermigkis C, Bouloukaki I, Antoniou K, Papadogiannis G, Giannarakis I, Varouchakis G, Siafakas N, Schiza SE. Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis. *Sleep and Breathing* 2014.
75. Migita K, Arai T, Jiuchi Y, Izumi Y, Iwanaga N, Kawahara C, Suematsu E, Miyamura T, Tsutani H, Kawabe Y, Matsumura R, Mori S, Ohshima S, Yoshizawa S, Suenaga Y, Ogushi F, Kawabata M, Furukawa H, Matsui T, Bito S, Tohma S. Predictors of mortality in patients with interstitial lung disease treated with corticosteroids: results from a cohort study. *Medicine* 2014: 93(26): e175.
76. Mohamed AR, Shaban MM. Role of laser acupuncture in chronic respiratory diseases. Egyptian Journal of Chest Diseases and Tuberculosis, 2014; pp. 1065-1070.
77. Nishiyama O, Miyajima H, Fukai Y, Yamazaki R, Satoh R, Yamagata T, Sano H, Iwanaga T, Higashimoto Y, Nakajima H, Kume H, Tohda Y. Effect of ambulatory oxygen on exertional dyspnea in IPF patients without resting hypoxemia. *Respiratory Medicine* 2013: 107(8): 1241-1246.
78. Nolan CM, Patel S, Barker RE, George PM, Cullinan P, Maher TM, Maddocks MM, Man WDC. Are there differences in response to pulmonary rehabilitation (PR) in idiopathic pulmonary fibrosis (IPF) and COPD patients? *European Respiratory Journal* 2017: 50.
79. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE, Jr., Lancaster L, Sahn SA, Szwarcberg J, Valeyre D, du Bois RM, Group CS. Pirfenidone in patients with

idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011: 377(9779): 1760-1769.
80. Ogura T, Azuma A, Kim DS. Double-blind, controlled trial of PC-SOD in patients with idiopathic pulmonary fibrosis-evaluation of safety and tolerability following inhaled administration. Respirology (Carlton, Vic), 2015; p. 65.
81. Okuda R, Matsushima H, Oba T, Kawabe R, Matsubayashi M, Amano M, Nishizawa T, Honda K. Efficacy and safety of inhaled N-acetylcysteine in idiopathic pulmonary fibrosis: A prospective, single-arm study. *Respiratory Investigation* 2016: 54(3): 156-161.
82. Oltmanns U, Kahn N, Palmowski K, Trager A, Wenz H, Heussel CP, Schnabel PA, Puderbach M, Wiebel M, Ehlers-Tenenbaum S, Warth A, Herth FJ, Kreuter M. Pirfenidone in idiopathic pulmonary fibrosis: real-life experience from a German tertiary referral center for interstitial lung diseases. *Respiration* 2014: 88(3): 199-207.
83. Pan YY, Liu HG. [Sleep-disordered breathing in patients with idiopathic pulmonary fibrosis]. *Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih Chinese Journal of Tuberculosis & Respiratory Diseases* 2016: 39(6): 474-476.
84. Polo?ski L, Ku?nierz B, Krzywiecki A, Polo?ska A, Tendera M, Oklek K, Wodniecki J. Effects of long term oxygen therapy in patients with idiopathic pulmonary fibrosis. II. Effect of oxygen therapy on function of heart ventricles. Polskie archiwum medycyny wewnetrznej, 2017; pp. 337-341.
85. Raghu G, Behr J, Brown KK, Egan J, Kawut SM, Flaherty KR. ARTEMIS-IPF: A Placebo-Controlled Trial Of Ambrisentan In Idiopathic Pulmonary Fibrosis [Abstract]. American journal of respiratory and critical care medicine, 2012; p. A3632.
86. Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J. Efficacy And Safety Of Macitentan In Idiopathic Pulmonary Fibrosis: Results Of A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial [Abstract]. American journal of respiratory and critical care medicine, 2012; p. A3631.
87. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Nathan SD, Wells AU, Collard HR, Costabel U, Richeldi L, de Andrade J, Khalil N, Morrison LD, Lederer DJ, Shao L, Li X, Pedersen PS, Montgomery AB, Chien JW, O'Riordan TG, Investigators* A-I. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial.[Erratum appears in Ann Intern Med. 2014 May 6;160(9):658], [Summary for patients in Ann Intern Med. 2013 May 7;158(9):I-32; PMID: 23785719]. *Annals of Internal Medicine* 2013: 158(9): 641-649.
88. Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J, Group MS. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. *European Respiratory Journal* 2013: 42(6): 1622-1632.
89. Raghu G, Nathan SD, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Wells AU, Shao L, Zhou H, Henig N, Szwarcberg J, Gillies H, Montgomery AB, O'Riordan TG. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. *European Respiratory Journal* 2015: 46(5): 1370-1377.
90. Raghu G, Scholand MB, de Andrade J, Lancaster L, Mageto Y, Goldin J, Brown KK, Flaherty KR, Wencel M, Wanger J, Neff T, Valone F, Stauffer J, Porter S. FG-3019 anti-connective tissue growth factor monoclonal antibody: results of an open-label clinical trial in idiopathic pulmonary fibrosis. *European Respiratory Journal* 2016: 47(5): 1481-1491.
91. Raghu G, Brow n K, Collard H, Lederer D, Martinez F, Noble P, Song JW, Wells A, Whelan T, Moreau E, Patterson S, Bayly S, Chien J, Zhang J, O'Riordan T. Simtuzumab in idiopathic pulmonary fibrosis: Results of a randomized clinical trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
92. Raghu G, Brown KK, Collard HR, Cottin V, Gibson KF, Kaner RJ, Lederer DJ, Martinez FJ, Noble PW, Song JW, Wells AU, Whelan TP, Wuyts W, Moreau E, Patterson SD, Smith V, Bayly S, Chien JW, Gong Q, Zhang JJ, O'Riordan TG. Efficacy of simtuzumab versus placebo in patients with idiopathic pulmonary fibrosis: a randomised, double-blind, controlled, phase 2 trial. *The Lancet Respiratory Medicine* 2017: 5(1): 22-32.

93. Restivo MD, Podolanczuk A, Kawut SM, Raghu G, Leary PJ, Barr RG, Lederer DJ. Antacid Use And Subclinical Interstitial Lung Disease: The MESA Study. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
94. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Kluglich M, du Bois RM. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *New England Journal of Medicine* 2011: 365(12): 1079-1087.
95. Richeldi L, Du Bois R, Raghu G, Azuma A, Brown KK, Costabel U. Efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis: results of two 52-week, phase iii, randomized, placebo-controlled trials (INPULSIS?) (Abstract). American Journal of Respiratory and Critical Care Medicine, 2014; p. A6603.
96. Richeldi L, Du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U. Efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis: results of two 52-week, phase iii, randomized, placebo-controlled trials (INPULSIS?). Respirology (Carlton, Vic), 2014; p. 28.
97. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR, Investigators IT. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis.[Erratum appears in N Engl J Med. 2015 Aug 20;373(8):782; PMID: 26287867]. *New England Journal of Medicine* 2014: 370(22): 2071-2082.
98. Richeldi L, Costabel U, Selman M, Xu Z, Kimura T, Stowasser S. Efficacy and safety of nintedanib in patients with IPF beyond week 52: Data from the phase ii tomorrow trial. American Journal of Respiratory and Critical Care Medicine, 2015; p. A1019.
99. Richeldi L, Cottin V, du Bois RM, Selman M, Kimura T, Bailes Z, Schlenker-Herceg R, Stowasser S, Brown KK. Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS (R) trials. *Respiratory Medicine* 2016: 113: 74-79.
100. Ryerson CJ, Camp PG, Eves ND, Schaeffer M, Syed N, Dhillon S, Jensen D, Maltais F, O'Donnell DE, Raghavan N, Roman M, Stickland MK, Assayag D, Bourbeau J, Dion G, Fell CD, Hambly N, Johannson KA, Kalluri M, Khalil N, Kolb M, Manganas H, Moran-Mendoza O, Provencher S, Ramesh W, Rolf JD, Wilcox PG, Guenette JA. High Oxygen Delivery to Preserve Exercise Capacity in Patients with Idiopathic Pulmonary Fibrosis Treated with Nintedanib. Methodology of the HOPE-IPF Study. *Annals of the American Thoracic Society* 2016: 13(9): 1640-1647.
101. Saini G, McKeever T, Johnson S, Jenkins G. Thalidomide as treatment for IPF associated cough. *Thorax* 2011: 66: A103.
102. Sakamoto S, Muramatsu Y, Satoh K, Ishida F, Kikuchi N, Sano G, Sugino K, Isobe K, Takai Y, Homma S. Effectiveness of combined therapy with pirfenidone and inhaled N-acetylcysteine for advanced idiopathic pulmonary fibrosis: a case-control study. *Respirology* 2015: 20(3): 445-452.
103. Salem M, Diab A, Ateya A, Sanad O. Short term effects of sildenafil citrate therapy in secondary pulmonary hypertension. Egyptian Heart Journal, 2014; pp. 49-53.
104. Saunders P, Saini G, Marshall RP, Fahy WA, Duggan AM, Wells AU, Costa MJ, Oballa E, Lukey P, Braybrooke R, Molyneaux PL, Hubbard R, Maher TM, Jenkins RG. Cough Related Quality Of Life In Patients With Idiopathic Pulmonary Fibrosis - Initial Findings From The Profile Cohort. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
105. Scalori A, Belloni P, Ackrill A, Kapugampola L, Doyle R, Kaminski J. Lebrikizumab idiopathic pulmonary fibrosis trial: A phase II randomized, double-blind, placebo controlled study to assess efficacy and safety (RIFF). Respirology (Carlton, Vic), 2014; p. 145.
106. Schaeffer MR, Ryerson CJ, Wilkie SS, Ramsook AH, Molgat-Seon Y, Khalil N. Acute effects of supplemental oxygen on dyspnea, exercise endurance and respiratory neural drive in patients with fibrotic interstitial lung disease. American Journal of Respiratory and Critical Care Medicine, 2015; p. A4400.
107. Sgalla G, Cerri S, Ferrari R, Ricchieri MP, Poletti S, Ori M, Garuti M, Montanari G, Luppi F, Petropulacos K, Richeldi L. Mindfulness-based stress reduction in patients with interstitial lung

diseases: a pilot, single-centre observational study on safety and efficacy. *BMJ open respiratory research* 2015: 2(1): e000065.
108. Sgalla G, Ferrari R, Cerri S, Ricchieri MP, Ori M, Garuti M, Montanari G, Taddei S, Luppi F, Luca R. Mindfulness-based stress reduction in patients with interstitial lung disease: A pilot study. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2014: 44(no pagination).
109. Sharp C, McCabe M, Hussain MJ, Adamali H, Smith DL, Edwards A, Millar AB. Pulmonary rehabilitation in interstitial lung disease-a prospective, observational study. *Thorax* 2015: 70: A56-A57.
110. Sharp C, Adamali H, Millar AB. Ambulatory and short-burst oxygen for interstitial lung disease. *Cochrane Database of Systematic Reviews* 2016: 7: CD011716.
111. Shimizu Y, Shimoyama Y, Kawada A, Kusano M, Hosomi Y, Sekiguchi M, Kawata T, Horie T, Ishii Y, Yamada M, Dobashi K, Takise A. Gastrointestinal symptoms in idiopathic pulmonary fibrosis patients treated with pirfenidone and herbal medicine. *Journal of Biological Regulators & Homeostatic Agents* 2014: 28(3): 433-442.
112. Shulgina L, Cahn AP, Chilvers ER, Parfrey H, Clark AB, Wilson EC, Twentyman OP, Davison AG, Curtin JJ, Crawford MB, Wilson AM. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial. *Thorax* 2013: 68(2): 155-162.
113. Skovhus Prior T, Troelsen T, Hilberg O. Driving performance in patients with chronic obstructive lung disease, interstitial lung disease and healthy controls: a crossover intervention study. *BMJ open respiratory research* 2015: 2(1): e000092.
114. Soares RV, Forsythe A, Hogarth K, Sweiss NJ, Noth I, Patti MG. Interstitial lung disease and gastroesophageal reflux disease: key role of esophageal function tests in the diagnosis and treatment. *Arquivos de Gastroenterologia* 2011: 48(2): 91-97.
115. Suraj KP, Kumar NK, Jyothi E, Narayan KV, Biju G. Role of Pirfenidone in Idiopathic Pulmonary Fibrosis - A Longitudinal Cohort Study. *Journal of the Association of Physicians of India* 2016: 64(5): 36-41.
116. Taguchi Y, Ebina M, Hashimoto S, Ogura T, Azuma A, Taniguchi H, Kondoh Y, Suga M, Takahashi H, Nakata K, Sugiyama Y, Kudoh S, Nukiwa T, Pirfenidone Clinical Study Group in J. Efficacy of pirfenidone and disease severity of idiopathic pulmonary fibrosis: Extended analysis of phase III trial in Japan. *Respiratory Investigation* 2015: 53(6): 279-287.
117. Taniguchi H, Xu Z, Azuma A, Inoue Y, Li H, Fujimoto T. Subgroup analysis of asian patients in the Inpulsis trials of nintedanib in idiopathic pulmonary fibrosis. Respirology (Carlton, Vic), 2014; p. 30.
118. Taniguchi H, Xu Z, Azuma A, Inoue Y, Li H, Fujimoto T, Bailes Z, Schlenker-Herceg R, Kim DS. Subgroup analysis of Asian patients in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis. *Respirology* 2016: 21(8): 1425-1430.
119. Tonelli R, Cocconcelli E, Lanini B, Romagnoli I, Florini F, Castaniere I, Andrisani D, Cerri S, Luppi F, Fantini R, Marchioni A, Beghe B, Gigliotti F, Clini EM. Effectiveness of pulmonary rehabilitation in patients with interstitial lung disease of different etiology: a multicenter prospective study. *BMC Pulm Med* 2017: 17(1): 130.
120. Triantafillidou C, Manali E, Lyberopoulos P, Kolilekas L, Kagouridis K, Gyftopoulos S, Vougas K, Kotanidou A, Alchanatis M, Karakatsani A, Papiris SA. The Role of Cardiopulmonary Exercise Test in IPF Prognosis. *Pulmonary Medicine* 2013: 2013: 514817.
121. Troy L, Young I, Munoz P, Taylor N, Webster S, Lau E. Does supplemental oxygen increase exercise endurance in patients with idiopathic pulmonary fibrosis? [Abstract]. Respirology (Carlton, Vic), 2014; p. 95 [tp 116].
122. Troy L, Wong K, Taylor N, Yee B, Corte P, Torzillo P. Supplemental oxygen improves sleep disordered breathing in patients with interstitial lung disease. Respirology (Carlton, Vic), 2015; p. 58 [to 117].

123. Tzouvelekis A, Paspaliaris V, Koliakos G, Ntolios P, Bouros E, Oikonomou A, Zissimopoulos A, Boussios N, Dardzinski B, Gritzalis D, Antoniadis A, Froudarakis M, Kolios G, Bouros D. 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. *Journal of Translational Medicine* 2013: 11: 171.
124. Vainshelboim B, Oliveira J, Fox B, Soreck Y, Kramer M. Physical activity following 12-week supervised exercise training program in patients with idiopathic pulmonary fibrosis. European Respiratory Journal, 2015.
125. Vieira T, Belchior I, Almeida J, Hespanhol V, Winck JC. [Efficacy and patterns of ambulatory oxygen usage - experience of a university hospital]. *Revista Portuguesa de Pneumologia* 2011: 17(4): 159-167.
126. Vitale C, Lanza M, Calabrese G, Caccavo G, D'Amato M, Stanziola AA. Idiopathic pulmonary fibrosis treatment: Combined pirfenidone + acetylcysteine vs N-acetylcysteine in monotherapy [Abstract]. European Respiratory Journal, 2014; p. P4502.
127. Watanabe N, Taniguchi H, Kondoh Y, Kimura T, Kataoka K. [Clinical efficacy of sildenafil in interstitial pneumonia with pulmonary hypertension]. *Nihon Kokyuki Gakkai Zasshi* 2011: 49(3): 151-155.
128. Wilson EC, Shulgina L, Cahn AP, Chilvers ER, Parfrey H, Clark AB, Twentyman OP, Wilson AM. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: an economic evaluation alongside a randomised controlled trial. *Pharmacoeconomics* 2014: 32(1): 87-99.
129. Parisien-La Salle S, Abel Rivest E, Gosselin Boucher V, Lalande-Gauthier M, Morisset J, Manganas H, Poirier C, Comtois A-S, Dube B-P. Effects of Pursed Lip Breathing on Exercise Capacity and Dyspnea in Patients With Interstitial Lung Disease: A RANDOMIZED, CROSSOVER STUDY. *Journal of cardiopulmonary rehabilitation and prevention* 2019.
130. Sciriha A, Lungaro-Mifsud S, Fsadni P, Scerri J, Montefort S. Pulmonary Rehabilitation in patients with Interstitial Lung Disease: The effects of a 12-week programme. *Respiratory Medicine* 2019: 146: 49-56.
131. Naz I, Sahin H, Ucsular FD, Yalniz E. A comparison trial of eight weeks versus twelve weeks of exercise program in interstitial lung diseases. *European Respiratory Journal* 2017: 50.
132. Ochman M, Maruszewski M, Latos M, Jastrzebski D, Wojarski J, Karolak W, Przybyfowski P, Zeglen S. Nordic Walking in Pulmonary Rehabilitation of Patients Referred for Lung Transplantation. *Transplantation Proceedings* 2018: 50(7): 2059-2063.
133. Perez-Bogerd S, Wuyts W, Barbier V, Demeyer H, Van Muylem A, Janssens W, Troosters T. Short and long-term effects of pulmonary rehabilitation in interstitial lung diseases: a randomised controlled trial. *Respir Res* 2018: 19(1): 182.
134. Camcioglu B, Guclu MB, Keles MN, Oskay D, Turktas H. Effects of neuromuscular electrical stimulation on functional exercise capacity, respiratory and peripheral muscle strength in patients with interstitial lung disease: A preliminary report. *European Respiratory Journal* 2017: 50.
135. Koczulla R, Koelpin J, Kaufhold F, Vogelmeier C, Herth FJF, Boeselt T, Alter P, Kahler C, Veith M, Greulich T, Kreuter M. Effects Of 3-Months Whole-Body Vibration Training On Muscle Strength, Lung Function Parameters, Health-Related Quality Of Life And Markers Of Inflammation In Patients With Interstitial Lung Disease At Three Different Centers For Lung Research (dzl) In Germany. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
136. Kondoh Y, Taniguchi H, Kataoka K, Arizono S, Ogawa T, Watanabe F, Kozu R, Nishimura K, Nishiyama O, Ogura T, Saka H. Long-Term Effect Of Pulmonary Rehabilitation Under Nintedanib Treatment In Idiopathic Pulmonary Fibrosis: Methodology Of The Fitness Study. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
137. Lam K, Breiburg A, Kuschner W, Zone C, Dhillon G. Long-Term Impact Of Non Invasive Open Ventilation (niovtm) On Dyspnea In Patients With Chronic Obstructive Pulmonary Disease And Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.

138. Matsuda Y, Morita T, Miyaji T, Taniguchi Y, Naoki Y, Maekura T, Nakao K, Tokura S, Tokoro A, Yamaguchi T, Iwase S, Inoue Y. Phase 1 Study Of Safety Of Morphine For Dyspnea In Patients With Interstitial Lung Diseases: Jortc-Pal05 Study. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
139. Al Aghbari J, Wong K, Lau E, Taylor N, Webster S, Yee B. Supplemental oxygen improves sleep disordered breathing but not quality of life in patients with interstitial lung disease. Respirology (Carlton, Vic), 2016; p. 147 [tp 115].
140. Koulopoulou M, Chua F, Koutoumanou E, Narayan S, Nikoletou D. Inspiratory muscle training (IMT) in interstitial lung disease (ILD) - A pilot study. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
141. Koulopoulou M, Greenwood S, Reilly C, Chua F. Feasibility of an 8-week out-patient inspiratory muscle training (IMT) programme in patients with interstitial lung disease (ILD). *Thorax Conference: british thoracic society winter meeting 2016 United kingdom Conference start: 20161207 Conference end: 20161209* 2016: 71: A240.
142. Nykvist M, Skold M, Ferrara G, Faager G. Inspiratory muscle training in addition to physical exercise for idiopathic pulmonary fibrosis. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
143. Stanley L, Cobbett C, Morris E, Gibson D, Fletcher SV. Pulmonary rehabilitation (PR) for interstitial lung disease (ILD). Do patients' perceptions match functional outcomes? *Thorax* 2016: 71: A240-A241.
144. Stessel M, Wapenaar M, Huremovic J, Bendstrup E, Molina M, Wijsenbeek M. The efficacy of a walk-bike on quality of life and exercise capacity in patients with idiopathic pulmonary fibrosis (IPF). A pilot study. European Respiratory Journal, 2015.

Suppl 3 Detailed study PICOS

Study	Summary of intervention details	Participant details and key eligibility criteria	Summary of relevant Outcomes
Pharmacological			
Bosentan			
Corte et al, 2014[1] Linked to Keir et al, 2013[2] **Country:** UK **Language:** English **Source of funding:** commercial and non-commercial **Study design:** RCT **Number of centres:** 8 **Trial ID:** NCT00637065 (no results posted) **Objectives of study:** To evaluate the safety and clinical efficacy bosentan in people with pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia.	**Intervention:** bosentan, orally twice daily, 62.5mg up titrated to 125mg after 1 month. **Placebo or control:** placebo **Duration:** 16 weeks **Modifications:** not reported **Concurrent treatments:** supplemental oxygen for resting, nocturnal, and/or exercise hypoxemia as appropriate	**Study inclusion criteria**: 18–80 years; diagnosis of IPF or idiopathic fibrotic nonspecific interstitial pneumonia (according to multidisciplinary consensus at a specialist ILD referral centre and in concordance with ATS/ERS 2002) and pulmonary hypertension (PH). **Study exclusion criteria:** significant hepatic or renal impairment, a greater extent of emphysema than interstitial change on high-resolution CT, clinically overt ischemic heart disease. No PAH-specific treatments were permitted for at least 3 months before enrollment. **No. of participants enrolled:** total 60; bosentan 40; placebo 20 **No. of participants included in analysis:** total 39; bosentan 25; placebo 14 **No. completing study:** total 40; bosentan 26; placebo 14 **Reasons for withdrawals:** bosentan (3 protocol violation, 5 serious adverse events, 3 deaths, 2 withdrawal of consent, 1 disease progression); placebo (1 protocol violation, 3 deaths, 1 withdrawal of consent, 1 lung transplant). Text states 1 placebo participant had a serious adverse event but this doesn't concur with figure or table. In addition, I participant in the bosentan group had no RHC data available	**Outcome measures:** 6MWT Quality of life (Cambridge Pulmonary Hypertension Outcome Review [CAMPHOR] questionnaire), described as a QoL measure but reports symptoms as a subscale which was data extracted. **Methods of statistical analysis used:** per protocol analysis **Handling of missing data:** no substitution for missing data **Follow-up duration**: 16 weeks
King et al, 2011[3] **Country:** USA **Language:** English **Source of funding:** commercial **Study design:** RCT **Number of centres:** 119 centres in 19 countries	**Intervention:** bosentan, orally twice daily, 62.5mg up titrated to 125mg after 1 month. Bosentan, orally twice daily, 62.5 mg up titrated to 125mg after 1 month (or remaining at 62.5 mg twice daily if body weight<40 kg).	**Study inclusion criteria**: >18years; diagnosis of IPF according to ATS/ERS 2000 of < 3 years duration, and diagnosis confirmed by surgical lung biopsy. **Study exclusion criteria:** extensive honeycombing on base-line high-resolution computed tomography (HRCT). Others as specified in the study.	**Outcome measures:** Primary Time to occurrence of IPF worsening or death Secondary HRQoL (SF-36, EQ 5D)

Trial ID: NCT00391443 **Objectives of study:** to demonstrate that bosentan delays IPF worsening or death.	**Placebo or control:** placebo **Duration:** from trial entry to BUILD-3 end of study, which was declared after 252 morbidity–mortality events **Modifications:** not reported **Concurrent treatments:** supplemental oxygen received by 12.3% in the bosentan group and 11% in placebo group	**No. of participants enrolled:** total 616; bosentan 407; placebo 209 **No. of participants included in analysis:** total 616; bosentan 407; placebo 209 **No. completing study:** total 521; bosentan 333; placebo 188 **Reasons for withdrawals:** adverse events (14.8% bosentan, 6.2% placebo), withdrawal of consent(2.5% bosentan, 1.0% placebo), investigator decision (0.7% bosentan, 1.0% placebo), or lung transplant (0.25% bosentan, 1.9% placebo)	Dyspnoea (Transition Dyspnoea Index) Pulmonary function test Safety and tolerability of bosentan **Methods of statistical analysis used:** ITT **Handling of missing data:** no imputation for missing data. However, censoring for time to death up to end of study in patients without an event was performed using the latest available measurements. For other endpoints, the last post-baseline observation carried forward was used except for IPF worsening or death. In cases of IPF worsening or death, the worst post-baseline value derived or observed at 1 year was used for changes from baseline to 1 year in HRQoL and FVC. For TDI and changes in DLCO at 1 year the fixed values (−9 for TDI, 1 mmol·kPa−1 ·min−1 for DLCO) were used. **Follow-up duration**: from trial entry to BUILD-3 end of study, which was declared after 252 morbidity–mortality events
King et al, 2008[4] **Country:** USA **Language:** English **Source of funding:** commercial	**Intervention:** bosentan, orally twice daily, 62.5mg up titrated to 125mg twice daily after 1 month.	**Study inclusion criteria**: diagnosis of IPF within the last 3 years according to ATS/ERS 2000/2002 criteria; HRCT scan used to demonstrate a definitive diagnosis of IPF. If diagnosis could not be confirmed based on HRCT	**Outcome measures:** Primary: 6MWT

Study design: RCT **Number of centres:** 29 **Trial ID:** NCT00071461 **Objectives of study:** To determine the effects of bosentan on exercise capacity and time to disease progression in patients with IPF.	**Placebo or control:** placebo **Duration:** 12 months **Modifications:** not reported **Concurrent treatments:** supplemental oxygen received by 23% in the bosentan group and 15.5% in placebo group	scan, a surgical lung biopsy was used; duration of illness 3 months or more and baseline 6MWD between 150 and 499m. **Study exclusion criteria:** ILD due to conditions other than IPF, severe restrictive lung disease (FVC < 50% pred); DLCO, corrected for haemoglobin level < 30% pred; or RV ≥ 120%, obstructive lung disease (FEV1/FVC < 65%), echocardiographic evidence of severe pulmonary hypertension (systolic pulmonary pressure ≥ 50 mm Hg or tricuspid regurgitation velocity ≥ 3.2 m/s), severe CHF, or a terminal (expected survival < 1 yr) concomitant illness. Other exclusion criteria included an FVC of 90% pred or greater, resting PaO2 of < 55 mm Hg (sea level) or 50 mm Hg (above 1,400 m), haemoglobin concentration < 75% of the lower limit of normal, systolic BP < 85 mm Hg, moderate to severe hepatic impairment, and serum creatinine of 2.5 mg/dl or greater. Concomitant treatment with immunosuppressive, cytotoxic drugs or other investigational agents was not allowed, except for stable corticosteroid therapy of 15 mg or less of prednisone or equivalent. Other prohibited medications included calcineurin inhibitors, fluconazole, and glyburide, due to potential interactions with bosentan. **No. of participants enrolled:** total 158; bosentan 74; placebo 84 **No. of participants included in analysis:** total 154; bosentan 71; placebo 83 **No. completing study:** total 109; bosentan 49; placebo 60 **Reasons for withdrawals:** 49 patients discontinued study medication before Month 12, mainly due to adverse events or disease progression (n = 39). Other reasons were withdrawal of consent by the patient (n = 9) and transplant (n = 1). No patient was lost to follow-up.	Secondary Time to disease progression or death PFT scores Dyspnoea scores QoL (SF-36, SGRQ) Safety **Methods of statistical analysis used:** ITT **Handling of missing data:** For patients with missing values, the analysis was performed with the last observation carried forward; an imputed value of zero was given in case of disease progression or death. Imputation values were identified before breaking treatment blinding **Follow-up duration**: 12 months
Sildenafil			

Jackson et al, 2010[5] **Country:** USA **Language:** English **Source of funding:** Non-commercial **Study design:** RCT **Number of centres:** 1 **Trial ID:** NCT00359736 **Objectives of study:** To examine the effects of sildenafil on 6MWD and Borg dyspnoea index in patients with IPF	**Intervention:** Sildenafil tablet orally, 20mg daily for 3 days, 20mg twice daily for 3 days, 20mg three times daily for the remainder of the trial **Placebo or control:** Placebo **Duration:** 6 months **Modifications:** Not reported **Concurrent treatments:** Patients used supplemental oxygen to maintain pre-exercise oxygen saturation at 90% or greater if needed.	**Study inclusion criteria**: IPF diagnosed using ATS/ERS 2002 criteria; 21 to 85 years; see table 1 in the study for other inclusion criteria **Study exclusion criteria:** echocardiographic evidence of severe pulmonary hypertension; severe heart failure; see table 1 in the study for other exclusion criteria **No. of participants enrolled:** total 29; sildenafil 14; placebo 15 **No. of participants included in analysis:** total 29; sildenafil 14; placebo 15 **No. completing study:** total 25: sildenafil 11; placebo 14 **Reasons for withdrawals:** Sildenafil group: adverse events (n = 2), impaired mobility (n = 1). Placebo group: adverse events (n = 1)	**Outcome measures:** Primary outcome 6MWD Secondary outcome Arterial oxygen saturation Pulmonary function tests Estimated pulmonary artery pressures Time to exhaustion on standardised bicycle testing **Methods of statistical analysis used:** ITT **Handling of missing data:** Missing data included in analysis but details not provided **Follow-up duration**: 6 months

Zisman et al, 2010[6] **Country:** USA **Language:** English **Source of funding:** commercial and non-commercial **Study design:** RCT **Number of centres:** 14 **Trial ID:** NCT00517933 **Objectives of study:** To test the hypothesis that treatment with sildenafil would improve walk distance, dyspnoea and quality of life in patients with advanced IPF	**Intervention:** Period 1: oral Sildenafil (20mg three times daily) for 12 weeks, followed by Period 2: a 12-week open-label extension with all patients receiving sildenafil **Placebo or control:** Placebo **Duration:** 12 weeks (primary outcome measured at end of period 1) **Modifications:** Not reported **Concurrent treatments:** 31% of patients in the sildenafil group and 26% in the placebo group used supplemental oxygen during walk test	**Study inclusion criteria**: diagnosis of IPF by consensus criteria, in an advanced stage defined as DLCO < 35% predicted. **Study exclusion criteria:** 6MWD < 50m (164ft); a difference of more than 15% in the 6MWD between two pre-randomisation walks; an extent of emphysema greater than the extent of fibrotic change as determined by HRCT scan; treatment with medications containing nitrates; presence of aortic stenosis or idiopathic hypertrophic subaortic stenosis; initiation of pulmonary rehabilitation within 30 days after screening; initiation or change in the dose of any investigational treatment for IPF within 30 days after screening; treatment for pulmonary hypertension with prostaglandins; endothelin-1 antagonists or other phosphodiesterase inhibitors within 30 days after screening; resting 0_2 saturation < 92% while breathing 6 L of supplemental O_2; being listed on an active waiting list for lung transplantation. **No. of participants enrolled:** total 180: sildenafil 89; placebo 91 **No. of participants included in analysis:** total 180 (included in primary analysis): sildenafil 89; placebo 91 **No. completing study:** total 143: sildenafil 73; placebo 70 **Reasons for withdrawals:** Sildenafil group: did not continue in the study in period 1 (n = 8) due to adverse events (n = 4), death (n = 2), lost to follow-up (n = 2); did not continue in the study after period 1 (n = 2); did not continue in the study in period 2 (n = 6) due to adverse events (n = 2), death (n = 2), withdrawn by investigator (n = 1), withdrew consent (n = 1). Placebo group: did not continue in the study in period 1 (n = 6) due to adverse events (n = 4), death (n = 1), lung transplantation (n = 1); did not continue in the study after period 1 (n = 2); did not continue in the study in period 2 (n = 13) due to adverse events (n = 4), death (n = 4), lung	**Outcome measures:** Primary outcome Presence or absence of an improvement of at least 20% in the 6MWD at 12 weeks Secondary outcomes Changes in the 6MWD Dyspnoea (University of California San Diego Shortness of Breath Questionnaire and the Borg Dyspnoea Index) Quality of life (St Georges Respiratory Questionnaire, SF-36 and EQ-5D) Change in forced vital capacity, carbon monoxide diffusion capacity, arterial partial pressure of oxygen and arterial oxygen saturation and the alveolar-arterial oxygen gradient while breathing ambient air Adverse events Hospitalisations Deaths **Methods of statistical analysis used:** ITT **Handling of missing data:** In the ITT, patients were deemed to have had no response if the rate of improvement was < 20% at 12 weeks or if they died, withdrew from the study or had missing data. **Follow-up duration**: 12 weeks for primary analysis

		transplantation (n = 2), withdrew consent (n = 3).	
Collard et al, 2007[7] **Country:** USA **Language:** English **Source of funding:** non-commercial **Study design:** Before and After **Number of centres:** 1	**Intervention:** Sildenafil (dosed between 20 and 50mg three times daily, depending on the formulation available) **Placebo or control:** Not applicable **Duration:** 12 weeks	**Study inclusion criteria**: IPF diagnosis according to ATS/ERS criteria 2000 and evidence of pulmonary hypertension defined by either a mean pulmonary artery (PA) pressure of $\geq$ 25mmHg on right-heart catheterisation or a PA systolic pressure of $\geq$ 35mmHg on echocardiography.	**Outcome measures:** Primary outcome Change in 6MWD Secondary outcomes Clinically meaningful response to sildenafil (defined

Trial ID: ID for RCT (NCT00352482) from which patients were transitioned into this study **Objectives of study:** To test the hypothesis that treatment with sildenafil would improve 6MWD in patients with IPF and pulmonary hypertension	**Modifications:** Not reported **Concurrent treatments:** Not reported	**Study exclusion criteria:** Patients with contraindications to phosphodiesterase inhibitor **No. of participants enrolled:** 14 **No. of participants included in analysis:** 11 **No. completing study:** 11 **Reasons for withdrawals:** chest pain during follow up 6MWT (n = 1), diarrhoea (n = 1), transient hypotension (n = 1)	as a $\geq$ 20% improvement in 6MWD) Incidence of adverse events **Methods of statistical analysis used:** Completer analysis **Handling of missing data:** excluded from analysis **Follow-up duration**: 12 weeks
Chinese medicine			
Zeng et al, 2015[8] **Country:** China **Language:** English **Source of funding:** Not reported **Study design:** RCT **Number of centres:** Not reported **Trial ID:** Not reported **Objectives of study:** to evaluate the impact of traditional Chinese medicine foot bath combined with traditional Chinese and western medicine nursing on patients with IPF.	**Intervention** **Blank group:** traditional Chinese and western medicine treatment **Foot bath group:** traditional Chinese medicine foot bath **Traditional Chinese medicine foot bath group:** Oral Chinese medicine and traditional Chinese medicine foot bath treatment **Combined group:** traditional Chinese and western medicine nursing under the precondition of traditional Chinese medicine foot bath group **Duration:** 6 months **Modifications:** Not reported **Concurrent treatments:** Not reported	**Study inclusion criteria**: Not reported **Study exclusion criteria:** Not reported **No. of participants enrolled:** 120; 30 patients in each group **No. of participants included in analysis:** Not reported **No. completing study:** Not reported **Reasons for withdrawals:** Not reported	**Outcome measures:** Anxiety, depression, pulmonary function, life quality and other indexes of patients **Methods of statistical analysis used:** Not reported **Handling of missing data:** Not reported **Follow-up duration**: 6 months
Yu et al, 2016[9] **Country:** China **Language:** English **Source of funding:** Non-commercial	**Intervention:** Feiwei granules, 2 bags twice a day (=32g per day). (Pharmaceutical Centre of Beijing China-Japan Friendship Hospital) Each 8-g bag of FG contained Xiyangshen	**Study inclusion criteria**: IPF diagnosed according to Chinese Thoracic Society criteria 2002; diagnosed as having "lung-kidney deficiency, Qi deficiency with blood stasis" according to Traditional Chinese Medicine (TCM) principles;	**Outcome measures:** Primary outcome not stated. MRC Dyspnoea scales SGRQ 6MWT

Study design: RCT **Number of centres:** 5 **Trial ID:** Not reported **Objectives of study:** to document the therapeutic effects of Feiwei granules for IPF.	(Radix Panacis Quinquefolii), Sanqi (Radix Notoginseng), Shanzhuyu (Fructus Macrocarpii), Wuweizi (Fructus Schisandrae Chinensis), Ziwan (Radix Asteris Tatarici), Maidong (Radix Ophiopogonis Japonici), Baiguo (Semen Ginkgo), and stir-frying with liquid adjuvant Gancao (Radix Glycyrrhizae). **Placebo or control:** Control Jinshuibao capsules, 3 capsules 3 times a day (Jiminkexin Pharmaceuticals, Jiangxi, China). **Duration:** 6 months **Modifications:** Not reported **Concurrent treatments:** Prednisone 0.5 mg/kg body weight (q.i.d.) in 1st month, 0.4 mg/kg (q.i.d.) in 2nd month, 0.3 mg/kg (q.i.d.) in 3rd month, then they maintained on 10 mg/day for the next 9 months. Unclear when this started, as study duration was 6 months. No other medical interventions for IPF permitted.	disease severity mild-to moderate; aged 18-70 years. **Study exclusion criteria:** other primary pulmonary diseases; use of TCM preparations to regulate and supplement their lungs and kidneys, or taken other immune system- boosting drugs in the previous month; use of oral glucocorticoid drugs long-term; pregnant, planning to become pregnant or lactating; allergic; severe primary diseases of the heart, brain, digestive system, or hematopoietic system; partial pressure of oxygen (PO2) at rest ≤ 50 mmHg; participation in clinical studies in previous month. **No. of participants enrolled:** 100; Feiwei granules 80, control 20. **No. of participants included in analysis:** 77; Feiwei granules 62, control 15. **No. completing study:** 77; Feiwei granules 62, control 15. **Reasons for withdrawals:** 20 lost to follow-up, 3 excluded, reason not provided, groups not stated.	Adverse events Pulmonary function, Traditional Chinese Medicine Syndrome Score and blood gas analyses not extracted. **Methods of statistical analysis used:** Completers analysed **Handling of missing data:** Missing data excluded from analysis **Follow-up duration**: 6 months
Riociguat			
Nathan et al, 2017[10] **Country:** USA **Language:** English **Source of funding:** commercial **Study design:** RCT **Number of centres:** multicentre (number of centres not stated) **Trial ID:** NCT02138825 **Objectives of study:** to evaluate	**Intervention:** riociguat up to 2.5mg three times daily **Placebo or control:** placebo **Duration:** 26 weeks followed by open-label extension where all patients received riociguat	**Study inclusion criteria**: IIP patients and each of the following: diagnosis of pulmonary hypertension confirmed by right heart catheterisation; FVC ≥ 45% pred; 6MWD ≥ 150 to ≤ 450 m. **Study exclusion criteria:** not reported **No. of participants enrolled:** total 147: Riociguat 73; placebo 74	**Outcome measures:** Primary outcome 6MWD Secondary outcomes All-cause mortality Hospitalisation 15% decrease in 6MWD Worsening of WHO

the efficacy and safety of riociguat in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonia (IIP)	**Modifications:** riociguat dose was individually adjusted from 0.5mg three times daily, increasing by 0.5mg every 2 weeks up to a maximum of 2.5mg three times daily over 10 weeks. Patients continued riociguat at their optimal dose for another 16 weeks. This was followed by a long-term extension treatment phase with riociguat up to 2.5mg three times daily. **Concurrent treatments:** not reported	**No. of participants included in analysis:** unclear **No. completing study:** study was terminated early due to unfavourable risk: benefit ratio (more deaths and serious adverse events in the riociguat group. **Reasons for withdrawals:** 11 deaths in the blinded phase (8 riociguat, 3 placebo), 9 in the extension (1 former riociguat, 8 former placebo), increased serious adverse events (37% riociguat, 23% placebo in the blinded phase).	functional class Adverse events **Methods of statistical analysis used:** Unclear as not stated **Handling of missing data:** Not reported **Follow-up duration**: 26 weeks
Hoeper et al, 2013[11] **Country:** Germany **Language:** English **Source of funding:** Commercial **Study design:** before and after study (interim analysis) **Number of centres:** 5 **Trial ID:** NCT00694850 (study results not posted) **Objectives of study:** to assess safety and tolerability of riociguat in patients with pulmonary hypertension associated with interstitial lung disease and the preliminary effects of the drug on haemodynamics, blood gases and exercise capacity.	**Intervention:** riociguat (soluble guanylate cyclase stimulator) 3 times daily, titrated in 0.5mg every 2-weeks from 1mg to target of 2.5mg depending on systolic blood pressure (SBP) 1 hour prior to administration of the morning dose, see below. **Placebo or control:** not applicable **Duration:** 12 weeks (12 months for those in extension phase) **Modifications:** dose was increased if SBP was >100mmHg, maintained if SBP 90–100mmHg and reduced if SBP <90mmHg without symptoms of hypotension (e.g dizziness or syncope). Drug stopped if SBP <90 mmHg with clinical signs of hypotension and re-started after 24 h at a reduced dose (-0.5mg x3 daily). If resting heart rate increased >120 beats/min or SBP <80 mmHg then stopped permanently. **Concurrent treatments:** able to use oxygen during all study procedures including 6MWT, but required to maintain the same flow throughout the study.	**Study inclusion criteria**: ≥18 years, one of four types of ILD (IPF, non-specific interstitial lung disease (NSILD), scleroderma or sarcoidosis) which was stable for at least 3 months (definitions provided), total lung capacity ≤90% of the predicted value (≤80% of the predicted value in scleroderma), evidence of pulmonary hypertension (PH) from right heart catheterisation within 3 months of commencement of study (definitions of PH stated in the paper), on stable medication. **Study exclusion criteria:** previous or ongoing treatments for pulmonary hypertension (e.g prostanoids, endothelin receptor antagonists, PDE-5 inhibitors) or nitrates, advanced pulmonary fibrosis (defined), other clinically relevant lung diseases, severe congenital lung, thorax or diaphragm abnormalities, left ventricular dysfunction, symptomatic coronary heart disease. **No. of participants enrolled:** 23 **No. of participants included in analysis:** 22 (safety); 18 (efficacy); 9 extension study **No. completing study:** 18 (12 weeks); 9 (12 month extension) **Reasons for withdrawals:** up to 12 weeks: adverse events 4; did not receive study drug 1. Up to 12 months: adverse events 4, withdrawal of consent 1; unspecified 2, death 1, lung transplant 1	**Outcome measures:** Safety and tolerability (primary outcomes) 6MWD Modified Borg dyspnoea scores after 6MWT Quality of life (SF-36, EuroQOL) **Methods of statistical analysis used:** received at least one dose (safety) or study completers (efficacy) **Handling of missing data:** no imputation **Follow-up duration**: 12 weeks all participants (safety) or study completers (efficacy); 12 months (interim data) for those continuing in to the ongoing extension study.

Oxygen			
Visca et al, 2017[12] **Country:** UK **Language:** English **Source of funding:** non-commercial **Study design:** RCT (cross-over) **Number of centres:** **Trial ID:** NCT02286063 **Objectives of study:** to evaluate whether supplementary oxygen during routine daily activities improves quality of life	**Intervention:** ambulatory oxygen. **Placebo or control:** off oxygen **Duration:** 2 weeks **Modifications:** no details **Concurrent treatments:** no details	**Study inclusion criteria**: adults with fibrotic ILD (including fibrotic NSIP, fibrotic organising pneumonitis, and fibrotic hypersensitivity pneumonitis) SaO2 ≥ 94% at rest, dropping to ≤88% on 6MWT, stable symptoms during a 2 week run-in period. **Study exclusion criteria:** meeting criteria for long term oxygen therapy, including hypercapnoea, expected to change treatment during the course of the study, significant locomotor or communication difficulties and/or severe co-morbidities, sarcoidosis or connective tissue disease affecting the musculoskeletal system, current smokers, pregnancy **No. of participants enrolled:** total 84; oxygen 41; no oxygen 43 **No. of participants included in analysis:** unclear **No. completing study:** total 76 **Reasons for withdrawals:** respiratory death 2; respiratory hospitalisation 2, patient choice 3, 1 not reported	**Outcome measures:** Health status by King's Brief Interstitial Lung Disease Questionnaire (KBILD); 3 domains breathlessness and activities, chest symptoms and psychological. Serious adverse events Clinical trial record also states secondary outcomes which includes: Dyspnoea scores (San Diego shortness of breath questionnaire); Global assessment of change in walking ability and exertional breathlessness; SGRQ; HAD **Methods of statistical analysis used:** not reported **Handling of missing data:** not reported **Follow-up duration**: 2 weeks (from clinical trial record)
Schaeffer et al, 2017[13] **Country:** Canada **Language:** English **Source of funding:** non-commercial **Study design:** RCT (cross-over) **Number of centres:** **Trial ID:** NCT01781793 **Objectives of study:** to determine the effects of hyperoxia on exercise endurance as well as the intensity and qualitative dimensions of	**Intervention:** hyperoxia **Placebo or control:** room air **Duration:** not reported **Modifications:** no details **Concurrent treatments:** no details	**Study inclusion criteria**: adults with fibrotic ILD (including 55% IPF) **Study exclusion criteria:** not reported **No. of participants enrolled:** total 20; 11 with IPF **No. of participants included in analysis:** unclear **No. completing study:** not reported **Reasons for withdrawals:** not reported	**Outcome measures:** Dyspnoea borg units Leg discomfort borg units Physiological parameters **Methods of statistical analysis used:** not reported **Handling of missing data:** not reported **Follow-up duration**: not

exertional dyspnoea in patients with fibrotic ILD			reported
Corticosteroids			
Papiris et al, 2015[14] **Country:** Greece **Language:** English **Source of funding:** not reported **Study design:** cohort study (retrospective treatment category, followed up prospectively) **Number of centres:** one **Trial ID:** not reported **Objectives of study:** hypothesized that previous immunosuppression and the administration of high-dose steroids adversely affect IPF acute exacerbation outcome	**Intervention:** ever treated (prior to admission with steroids, immune-suppressants). Patients were previously treated with steroids (10–25 mg prednisone/day), one patient also had methotrexate. **Placebo or control:** never treated (prior to admission) **Duration:** not clear **Modifications:** not reported **Concurrent treatments:** immediate cessation of immunosuppression (if any), best supportive care, broad spectrum antimicrobials, evaluation to detect reversible causes of respiratory deterioration.	**Study inclusion criteria**: previously admitted with IPF [2011 ATS/ERS] and IPF acute exacerbations (IPF Clinical Research Networks Investigators consensus; unexplained worsening or development of dyspnoea within 30 days, new lung infiltrates and exclusion of any identifiable or treatable cause of lung injury). **Study exclusion criteria:** not stated **No. of participants enrolled:** 17; ever treated 11; never treated 6 **No. of participants included in analysis:** analysed by events not participants: 24; ever treated 12; never treated 12 **No. completing study:** 17; ever treated 11; never treated 6 **Reasons for withdrawals:** Not applicable	**Outcome measures:** not defined as outcomes but data presented for: 6MWD Survival (extracted as deaths) **Methods of statistical analysis used:** ITT **Handling of missing data:** not applicable **Follow-up duration**: not reported.
Fiorucci et al, 2008[15] **Country:** Italy **Language:** English **Source of funding:** not reported **Study design:** Before and after study **Number of centres:** one **Trial ID:** not reported **Objectives of study:** to compare efficacy, tolerability and impact on survival of three currently available therapeutic regimens (steroids alone, steroids plus cyclophosphamide, steroids plus colchicine) in mild to moderate IPF	**Intervention:** Group 1: prednisone 1mg/kg/day; Group 2: prednisone 0.5mg/kg/day plus cyclophosphamide 100mg/day; Group 3: prednisone 0.5mg/kg/day plus colchicine 1mg/day **Placebo or control:** not applicable **Duration:** 18 months **Modifications:** Group 1 received prednisone 1mg/kg/day for 4 weeks then 0.5mg/kg/day for 2 months followed by a gradual reduction to a maintenance dose of 20mg/day; Group 2 received prednisone	**Study inclusion criteria**: IPF diagnosed according to ATS/ERS 2000/2002 criteria. **Study exclusion criteria:** patients that do not meet inclusion criteria; DLCO $\leq$ 40% pred was considered to be evidence of advanced disease **No. of participants enrolled:** 30; Group 1: n = 11; Group 2: n = 9; Group 3: n = 10 **No. of participants included in analysis:** 30 **No. completing study:** 30 **Reasons for withdrawals:** Not reported	**Outcome measures:** Clinical Radiographic Physiologic (CRP) score Dyspnoea Side effects Survival rate **Methods of statistical analysis used:** not clear if all included patients were analysed **Handling of missing data:** not clear **Follow-up duration**: 18

	0.5mg/kg/day for 1 month, 0.25mg/kg/day for 2 months following a reduction similar to previous group plus oral cyclophosphamide 100mg/day; Group 3 received prednisone 0.5mg/kg/day (using same reduction protocol as for group 2) plus oral colchicine 1mg/day **Concurrent treatments:** not reported		months. Survival analysis was performed after 3 years from index visit
Hope-Gill et al, 2003[16] **Country:** UK **Language:** English **Source of funding:** commercial and non-commercial **Study design:** controlled clinical trial **Number of centres:** one **Trial ID:** not reported **Objectives of study:** to study cough response to capsaicin, substance P (SP) and bradykinin in 10 healthy control subjects and 10 patients with IPF	**Intervention:** oral prednisolone 40 – 60mg/day for at least 4 weeks **Placebo or control:** healthy volunteers **Duration:** 4 weeks **Modifications:** 10 IPF patients and 10 control subjects underwent an initial capsaicin cough challenge by compressed air–driven dosimeter. Two further capsaicin challenges were performed. Before starting ste-roid therapy, IPF patients underwent a capsaicin cough challenge followed by SP inhalation, and these tests were then repeated after 4 weeks of treatment. **Concurrent treatments:** Patients (not control) subjects were given 20 mg/day for 1 month before starting the study and continued this therapy for its duration to exclude subclinical gastroesophageal reflux (GER).	**Study inclusion criteria**: IPF diagnosed according to ATS/ERS 2002 criteria. **Study exclusion criteria:** respiratory tract infection within 1 month; history of smoking within 1 yr; postnasal drip, rhinitis or catarrhal symptoms; symptoms of GER; asthma or respiratory diseases besides IPS; angiotensin-converting enzyme inhibitor, bronchodilator, or nonsteroidal anti-inflammatory drug therapy; other major systemic illness. **No. of participants enrolled:** total: 16; IPF 6; Control 10 **No. of participants included in analysis:** total: 16 **No. completing study:** 16 **Reasons for withdrawals:** Not applicable	**Outcome measures:** Cough symptom severity (Visual Analogue Scale) **Methods of statistical analysis used:** Included all patients **Handling of missing data:** not applicable **Follow-up duration**: 4 weeks
Proton pump inhibitor			
Dutta et al, 2019[17] **Country:** UK **Language:** English **Source of funding:** non-commercial **Study design:** RCT	**Intervention:** omeprazole 20mg twice daily **Placebo or control:** placebo **Duration:** 90 days	**Study inclusion criteria**: Participants aged 40–85 years with IPF recruited from the ILD clinic. Also, referrals from one of six Participant Identification Centres (PICs) by their treating clinicians. Participants were required to fulfil all of the following criteria: IPF considered the most likely diagnosis by the regional ILD	**Outcome measures:** Primary feasibility outcomes comprised number of eligible patients, the proportion of those willing to take part, the recruitment rate, adherence to

Number of centres: one **Trial ID:** NCT02085018 **Objectives of study:** This study aimed to determine the feasibility of a larger, multicentre trial of omeprazole for cough in IPF, to assess safety and to quantify cough.	**Modifications:** not reported **Concurrent treatments:** Patients taking antacids, prokinetics or raft alginates were eligible if they had been off these treatments for at least 2 weeks. Patients taking a regular PPI who wished to take part were eligible if they provided written informed consent to a 2-week trial period off treatment, following agreement with their general practitioner, and if the trial was tolerated and completed with no significant return of upper gastrointestinal (GI) symptoms such as reflux, indigestion or heartburn. Patients were asked to refrain from using over the counter antacids and to contact the study team if these were used.	multidisciplinary team; history of cough; radiological features of honeycombing in a predominantly basal and subpleural distribution on high-resolution CT (HRCT) scanning; bibasal inspiratory crackles on auscultation and features of a restrictive ventilatory defect (VC) <90% predicted and/or transfer factor for carbon monoxide (TLco) <90% predicted). **Study exclusion criteria:** Participants taking warfarin, diazepam, phenytoin or ketoconazole. Participants on IPF treatment had to have been taking these for at least 4 weeks before entry to the study. Other exclusion criteria included upper or lower respiratory tract infection or exacerbation of IPF in the 4 weeks prior to starting trial treatment, or a history of hepatic cirrhosis. **No. of participants enrolled:** 45 **No. of participants included in analysis:** **No. completing study:** 40 **Reasons for withdrawals:** death 1, withdrawn by investigator 2, protocol deviation 1, intolerance to placebo 1.	trial medication and follow-up and the acceptability of invasive trial procedures. Primary clinical outcome was cough frequency. Secondary outcomes included patient-reported symptoms of cough using the Leicester Cough Questionnaire (LCQ) and reflux (using the De Meester reflux-related symptoms questionnaire (DeMRQ) and the Reflux Symptoms Index (RSI)). **Methods of statistical analysis used:** Analysis of all clinical outcomes was performed on a complete-case basis following the ITT principle **Handling of missing data:** No imputation of missing data **Follow-up duration**: 90 days
Kilduff et al, 2014[18] **Country:** UK **Language:** English **Source of funding:** not reported **Study design:** Before and after study **Number of centres:** one **Trial ID:** not reported **Objectives of study:** to investigate the impact of high-dose acid suppressant therapy on gastroesophageal reflux (GOR) and cough in this condition	**Intervention:** high dose proton pump inhibitor therapy (omeprazole 40 mg twice daily or lansoprazole 30 mg twice daily) plus ranitidine 300 mg nocte **Placebo or control:** not applicable **Duration:** 8 weeks **Modifications:** not reported **Concurrent treatments:** All acid suppression and prokinetic medication withheld for ≤ one week prior to study assessment. 3 participants received additional prokinetic therapy	**Study inclusion criteria**: consecutive non-smoking patients meeting ATS/ERS IPF criteria 2002 **Study exclusion criteria:** Other causes of cough, except gastroesophageal reflux **No. of participants enrolled:** 18 **No. of participants included in analysis:** 14 **No. completing study:** 14 **Reasons for withdrawals:** 4 withdrew consent	**Outcome measures:** reflux events; 24-hour cough count data **Methods of statistical analysis used:** Not reported **Handling of missing data:** Not reported **Follow-up duration**: 8 weeks (immediately after intervention)

	(metoclopramide or domperidone).		
Thalidomide			
Horton et al, 2012[19] **Country:** USA **Language:** English **Source of funding:** commercial **Study design:** RCT (cross-over) **Number of centres:** 1 **Trial ID:** NCT00600028 **Objectives of study:** to determine the efficacy of thalidomide in suppressing cough in patients with IPF	**Intervention:** thalidomide, orally 50mg at bedtime, increased to 100mg if no improvement in cough occurred after 2 weeks **Placebo or control:** placebo **Duration:** patients received each treatment for 12 weeks in a crossover design with a 2-week washout period between the 2 treatments **Modifications:** not reported **Concurrent treatments:** to avoid the constipation associated with thalidomide, all participants received sodium docusate, 100mg by mouth daily, during the trial. All participants also received a daily vitamin B complex supplement	**Study inclusion criteria**: age > 50years with a clinical history consistent with IPF and chronic cough (cough of more than 8 weeks' duration). **Study exclusion criteria:** pregnancy, female sex with childbearing potential, toxic or environmental exposure to respiratory irritants, collagen vascular disease, airflow obstruction, active narcotic antitussive use, peripheral vascular disease or neuropathy, inability to give informed consent, allergy or intolerance to thalidomide or a life expectancy less than 6 months **No. of participants enrolled:** total 24; thalidomide 13; placebo 11. After 2-week washout period total 22; thalidomide 10; placebo 12 **No. of participants included in analysis:** total 20 **No. completing study:** total 20 **Reasons for withdrawals:** thalidomide group: lack of interest (n = 1), placebo group: worsening health (n = 1). After 2-week washout period thalidomide group: worsening health (n = 2)	**Outcome measures:** Primary outcome Cough Quality of Life Questionnaire (CQLQ) Secondary outcomes Cough (assessed by 10cm VAS) Respiratory QoL (SGRQ) **Methods of statistical analysis used:** cross-over trial. For each outcome measure, only the value at week 12 of thalidomide or placebo was used **Handling of missing data:** sensitivity analysis was carried out for missing data. Primary analysis was repeated by replacing missing CQLQ score with scores from day 0 and with the highest CQLQ score. **Follow-up duration**: total duration including a 2-week washout period was 26 weeks
Horton et al, 2008[20] **Country:** USA **Language:** English **Source of funding:** commercial **Study design:** Before and After **Number of centres:** 1 **Trial ID:** not reported **Objectives of study:** to assess if thalidomide is effective for cough associated with IPF	**Intervention:** thalidomide administered daily in 100 – 400mg doses **Placebo or control:** not applicable **Duration:** 3 months **Modifications:** not reported **Concurrent treatments:** not reported	**Study inclusion criteria**: patients with chronic cough caused by IPF **Study exclusion criteria:** not reported **No. of participants enrolled:** 11 **No. of participants included in analysis:** 10 **No. completing study:** 10 **Reasons for withdrawals:** lost to follow up (n = 1)	**Outcome measures:** Change in cough measured on the SGRQ **Methods of statistical analysis used:** completers **Handling of missing data:** excluded from analysis **Follow-up duration**: 3 months

PA101			
Birring et al, 2017[21, 22] **Country:** UK and Netherlands **Language:** English **Source of funding:** commercial **Study design:** RCT (cross-over) **Number of centres:** 7 **Trial ID:** NCT02412020 **Objectives of study:** to investigate the efficacy and safety of inhaled PA101 on chronic cough in IPF	**Intervention:** PA101 40 mg (cromolyn sodium via a high-efficiency nebuliser) 3 times daily **Placebo or control:** matching placebo **Duration:** 14 days then washout 14 days then 14 days cross over **Modifications:** not reported **Concurrent treatments:** Anti-fibrotic therapy (i.e., pirfenidone and nintedanib) if had taken a stable dose for at least 3 months prior to study start and remained on stable doses during the study	**Study inclusion criteria**: IPF (multidisciplinary team consensus based on definitive or possible usual interstitial pneumonia on high-resolution CT and exclusion of other lung diseases) with refractory cough (duration >8 weeks, not responsive to targeted therapies for possible underlying triggers (gastro-oesophageal reflux, asthma, rhinitis); aged 40-79 years, daytime cough severity ≥ 40 mm on a VAS, mean daytime objective cough frequency ≥15 coughs per hour on Leicester Cough Monitor (LCM), TLCOc > 25% of predicted value within 12 months and FVC > 50% of the predicted value within 1 month. **Study exclusion criteria:** presence of significant coronary artery disease (defined), upper or lower respiratory tract infection within 4 weeks, productive cough, acute exacerbation of IPF within 3 months, long-term daily oxygen therapy (>10 hours/day) and PAH with limitation of activity, taken (within 2 weeks of the study) prednisone, narcotic antitussives, gabapentin, inhaled corticosteroids, dextromethorphan, carbetapentane, H1 antihistamines, and cromolyn sodium. **No. of participants enrolled:** 24 **No. of participants included in analysis:** total 24; PA101 24; placebo 24 (analysed after cross over) **No. completing study:** total 22; PA101 23; placebo 23 **Reasons for withdrawals:** adverse events (2)	**Outcome measures:** Daytime cough frequency (from 24h LCM), primary outcome; subjective cough-specific QoL (Leicester Cough Questionnaire); K-BILD; Responders (>30% decrease in daytime cough frequency) Cough VAS and pulmonary function (not extracted) **Methods of statistical analysis used:** states ITT, details provided suggest modified ITT, states no period effect and presents data from combined periods 1 and 2. **Handling of missing data:** No imputation for missing data, analysis approach reported. **Follow-up duration**: immediately following 14 day treatment
VRP700			
Satia et al, 2014[23] **Country:** UK **Language:** English **Source of funding:** Not reported (1 author from commercial company) **Study design:** RCT (crossover) **Number of centres:** one	**Intervention:** single inhaled dose of VRP700 (100 mg) **Placebo or control:** placebo **Duration:** single dose for each intervention with a 7 day washout	**Study inclusion criteria**: patients with IPF with chronic cough **Study exclusion criteria:** Not reported **No. of participants enrolled:** 20 **No. of participants included in analysis:** Not reported	**Outcome measures:** number of coughs in 4 h (objective cough monitoring system, VitaloJAK, Vitalograph Ltd) (primary outcome) Urge to cough VAS, cough severity VAS, dyspnoea VAS

Trial ID: Not reported **Objectives of study:** to investigate the efficacy of VRP700 in reducing cough frequency in patients with IPF	**Modifications:** Not reported **Concurrent treatments:** Not reported	**No. completing study:** Not reported **Reasons for withdrawals:** Not reported	**Methods of statistical analysis used:** Not reported **Handling of missing data:** Not reported **Follow-up duration**: 24 hrs
Opioids			
Allen et al, 2005[24] **Country:** UK **Language:** English **Source of funding:** not reported **Study design:** before and after study **Number of centres:** 1 **Trial ID:** not reported **Objectives of study:** to observe whether any improvement in the degree of breathlessness reported was offset by significant adverse effects on basic vital signs and oxygen saturation immediately after starting treatment with diamorphine.	**Intervention:** Diamorphine was given subcutaneously at a dose of 2.5 mg to patients with a body weight of 60 kg or less, or 5 mg if over 60 kg (one patient). **Placebo or control:** not applicable **Duration:** 30 mins **Modifications:** not reported **Concurrent treatments:** supplemental oxygen was given as needed	**Study inclusion criteria**: Diagnosis of IPF; severe breathlessness; not receiving treatment with opioid drugs; and no significant cognitive impairment. **Study exclusion criteria:** not stated **No. of participants enrolled:** 11 **No. of participants included in analysis:** 11 **No. completing study:** 11 **Reasons for withdrawals:** not applicable	**Outcome measures:** Dyspnoea (analaogue scale) Heart rate (beats/min) Respiration rate (breaths/min) Systolic blood pressure (mmHg) Oxygen saturation (%) Survival **Methods of statistical analysis used:** all patients included in analysis **Handling of missing data:** not applicable **Follow-up duration**: 30 mins
Pulmonary rehabilitation / exercise training			
Chehere et al, 2019[25] **Country:** France **Language:** English **Source of funding:** not reported **Study design:** before and after **Number of centres:** 1 **Trial ID:** none **Objectives of study:** to investigate the effects of a pulmonary rehabilitation program on cardiorespiratory responses during a 6MWT and to identify the characteristics of patients who do not show improved performance	**Intervention:** Once a week, a health professional with expertise in exercise training and therapeutic education supervised a 90-min session in the patient's home. Patients were encouraged to carry out same exercises independently, with a target of five sessions/ week. Supervised sessions included exercise training, therapeutic patient education and psychosocial support based on an educational needs assessment. Supplemental oxygen was given if pulse O_2 saturation < 88%. **Placebo or control:** not applicable	**Study inclusion criteria**: IPF or NSIP diagnoses (ATS/ERS 2002/2013), resting pulse 0_2 saturation $\geq$ 88% **Study exclusion criteria:** participation in a pulmonary rehabilitation program in preceding year, receiving continuous 0_2 therapy, comorbidity precluding exercise training, FVC < 50% predicted, DLCO < 25% predicted. **No. of participants enrolled:** 21 **No. of participants included in analysis:** 19 **No. completing study:** 19 **Reasons for withdrawals:** Stopped pulmonary rehabilitation program 1; refused the second evaluation 1	**Outcome measures:** 6MWT SF-36 (quality of life) Baseline and Transition Dyspnea Index and 10-point Borg scale (dyspnea) HADS (anxiety and depression) Cardiorespiratory parameters (HR, VO_2, VCO_2, V_E, V_T, Bf, V_E/VO_2, V_E/VCO_2) **Methods of statistical analysis used:** study completers

after pulmonary rehabilitation.	**Duration:** 8 weeks **Modifications:** 79% had exercise 0_2 therapy support **Concurrent treatments:** not reported		**Handling of missing data:** not applicable **Follow-up duration**: 8 weeks
Nolan et al, 2018[26] **Country:** United Kingdom **Language:** English **Source of funding:** non-commercial **Study design:** before and after **Number of centres:** 3 **Trial ID:** none **Objectives of study:** to determine if improvement in 4MGS with pulmonary rehabilitation was associated with survival in people with idiopathic pulmonary fibrosis	**Intervention:** outpatient pulmonary rehabilitation **Placebo or control:** not applicable **Duration:** not reported **Modifications:** not reported **Concurrent treatments:** not reported	**Study inclusion criteria**: IPF (no further details) **Study exclusion criteria:** not reported **No. of participants enrolled:** 90 **No. of participants included in analysis:** not reported **No. completing study:** not reported **Reasons for withdrawals:** not reported	**Outcome measures:** Spirometry Anthropometry Four metre gait speed (4MGS) Incremental Shuttle Walk Test (ISW) King's Brief Interstitial Lung Disease (KBILD) questionnaire Mortality **Methods of statistical analysis used:** appeared not to be all enrolled patients **Handling of missing data:** not stated **Follow-up duration**: not reported
Del Castillo et al, 2017[27] **Country:** Colombia **Language:** English **Source of funding:** not reported **Study design:** before and after **Number of centres:** 1 **Trial ID:** none **Objectives of study:** to compare the benefits of pulmonary rehabilitation in patients with IPF and those with ILD of non-specific origin	**Intervention:** Continuous exercise on a treadmill for 30 – 40 minutes, initiating 60% of the estimated VO2 obtained in 6MWT, muscular strengthening and supplementary oxygen (total 24 sessions of 1 hour each). **Placebo or control:** not applicable **Duration:** 8 weeks **Modifications:** 56% used domiciliary oxygen	**Study inclusion criteria**: IPF diagnosis (no further details) **Study exclusion criteria:** not reported **No. of participants enrolled:** total 28; IPF (9 patients) **No. of participants included in analysis:** not reported **No. completing study:** not reported **Reasons for withdrawals:** not reported	**Outcome measures:** 6MWT MRC dyspnea HADS SGRQ questionnaire **Methods of statistical analysis used:** not reported **Handling of missing data:** not reported **Follow-up duration**: 8 weeks

	Concurrent treatments: not reported		
Dowman et al, 2017 [28-31] **Country:** Australia **Language:** English **Source of funding:** non-commercial **Study design:** RCT **Number of centres:** 3 **Trial ID:** ACTRN12611000416998. **Objectives of study:** to establish the impact of aetiology and severity of ILD on response to exercise training; identify an optimal time for exercise training to achieve maximal benefit.	**Intervention:** exercise training, twice weekly, supervised programme: 30 minutes aerobic exercise, cycling and walking, upper and lower limb resistance training. Exercise intensities stated and progressed weekly. Also a home exercise programme prescribed. Hospital training within a PR programme with educational component. **Placebo or control:** usual care, educational component of PR programme available, weekly telephone calls for general support. **Duration:** 8 weeks **Modifications:** not reported **Concurrent treatments:** Supplemental oxygen as necessary (used in 38%)	**Study inclusion criteria**: documented ILD (2011 ATS/ERS) who were clinically stable, ambulant, and reported dyspnoea on exertion despite maximal medical treatment **Study exclusion criteria:** concurrent and predominant respiratory disease other than ILD, a history of syncope on exertion, and any comorbidities that preclude exercise or participation in a supervised exercise programme within the previous 12 months **No. of participants enrolled:** total 142; exercise group 74; control 68 (IPF: 61, exercise 32, control 29) **No. of participants included in analysis:** unclear **No. completing study:** total 126 at 6 months. Exercise training: 49 participants completed the intervention but 66 were followed up; control 60	**Outcome measures:** 6MWD (primary outcome at 9 weeks) HRQoL by CRDQ and SGRQ-I (CRDQ dyspnea and fatigue only extracted) Dyspnea by UCSD SOBQ and modified MRC scale **Methods of statistical analysis used:** ITT **Handling of missing data:** not stated **Follow-up duration**: 6 months
Nolan et al, 2017[32] **Country:** United Kingdom **Language:** English **Source of funding:** non-commercial **Study design:** before and after study **Number of centres:** unclear **Trial ID:** none **Objectives of study:** to assess the responsiveness of the 4-metre gait speed (4MGS) in people with fibrotic ILD undergoing pulmonary rehabilitation (PR) and to estimate the minimum clinically important difference (MCID)	**Intervention:** outpatient pulmonary rehabilitation **Placebo or control:** not applicable **Duration:** 8 weeks **Modifications:** not reported **Concurrent treatments:** not reported	**Study inclusion criteria**: fibrotic ILD diagnoses (IPF n =67, NSIP n = 14, CHP n = 4, CT-ILD n = 4, PPFE n = 2, drug-induced ILD n = 2, FOP n = 1) **Study exclusion criteria:** not reported **No. of participants enrolled:** total 93: fibrotic ILD (81 patients) **No. of participants included in analysis:** unclear **No. completing study:** unclear **Reasons for withdrawals:** not reported	**Outcome measures:** Four metre gait speed (4MGS) Incremental Shuttle Walk Test (ISW) Chronic respiratory disease questionnaire (CRQ dyspnea and CRQ total) **Methods of statistical analysis used:** unclear **Handling of missing data:** not reported **Follow-up duration**: 8 weeks
Jarosch et al, 2016[33]	**Intervention:** inpatient PR programme. 5–6	**Study inclusion criteria**: IPF; age 50-80 years; FVC	**Outcome measures:**

Schneeberger et al, 2016[34] **Jarosch et al, 2017[35]** Additional information from study author. **Country:** Germany **Language:** English **Source of funding:** Commercial **Study design:** RCT **Number of centres:** **Trial ID:** not reported **Objectives of study:** to investigate short-term effects of an inpatient PR and sustainability after 3 months	exercise training sessions per week of 40–50 minutes. Physiotherapist supervised sessions of endurance training on cycle ergometers for 10–20 min, intensity progressing if possible to set target. Individually tailored strength training of 4 to 6 exercises with 3 x 20 repetitions and individual sessions of breathing strategies and practicing activities of daily life. Structured education sessions (twice weekly for 1 hour) and psychological support and nutritional education offered. **Placebo or control:** usual care control **Duration:** 3 weeks **Modifications:** not reported **Concurrent treatments:** not reported	>50% predicted; medical treatment according to recent guidelines **Study exclusion criteria:** general exclusion criteria for exercise training (acute coronary syndrome, acute myocarditis, lung embolism etc) **No. of participants enrolled:** total 51; PR 34; control 17 **No. of participants included in analysis:** not reported **No. completing study:** not reported **Reasons for withdrawals:** not reported	6MWD (primary outcome) SF-36 Chronic Respiratory Questionnaire (CRQ) (dyspnoea and fatigue subscales data extracted) **Methods of statistical analysis used:** appears to be study completers **Handling of missing data:** not applicable **Follow-up duration**: 3 months
Keyser et al, 2015[36, 37] **Country:** USA **Language:** English **Source of funding:** non-commercial **Study design:** before and after study **Number of centres:** three **Trial ID:** none (participants were from NCT00678821) **Objectives of study:** To characterize the cardiorespiratory response to exercise before and after aerobic exercise training in patients with interstitial lung disease	**Intervention:** aerobic exercise training (AET), supervised, treadmill walking 30–45 minutes per session (plus 5–10 minute warm-up), x3 per week. Target intensity 70–80% of heart rate. 1 hour education sessions (e.g anatomy and physiology, lung disease processes, medication use, oxygen therapy, relaxation techniques, breathing retraining, nutrition, and benefits of exercise) **Placebo or control:** not applicable **Duration:** 10 weeks programme. **Modifications:** Completion of 24 of the 30 training sessions was required to sustain participation in the program. **Concurrent treatments:** supplemental oxygen in 69%	**Study inclusion criteria**: New York Heart Association/World Health Organization (NYHA/WHO) Class II or III ILD, at least 21 years, physically inactive **Study exclusion criteria:** resting mean pulmonary arterial pressure of ≥25 mmHg; right or left ventricular ejection fractions <40% by echocardiography, significant repolarization abnormalities or arrhythmias; FEV1/FVC ratio <65%; ischemic heart disease, cardiomyopathy or left heart failure, right ventricular failure or cor pulmonale, pulmonary hypertension, hepatic or renal failure, (others listed), pregnancy, on antiretroviral therapy regimens, active smokers, admitting abuse of alcohol or other controlled or illegal substances, not participated in any form of regular aerobic exercise training, for at least 6 months. **No. of participants enrolled:** 13 **No. of participants included in analysis:** 13 **No. completing study:** 13	**Outcome measures:** 6MWT Fatigability index (from 6MWT) Fatigue Severity Scale **Methods of statistical analysis used:** ITT **Handling of missing data:** not applicable **Follow-up duration**: not stated, assume after 10 week intervention.

		Reasons for withdrawals: 13	
Rastogi et al, 2015[38] **Country:** India **Language:** English **Source of funding:** non-commercial **Study design:** before and after study **Number of centres:** 1 **Trial ID:** not reported **Objectives of study:** to determine whether PR is effective in improving the exercise capacity and dyspnoea scores of patients with ILD in a limited resource setting.	**Intervention:** individualised PR program included patient education and exercise training (endurance training (cycle ergometer and treadmill walking), strength training (weight cuffs, dumbbell), breathing and flexibility exercise (stretching); 3 sessions /week. Provided by a trained cardiopulmonary physiotherapist **Placebo or control:** not applicable **Duration:** 12 weeks **Modifications:** not reported **Concurrent treatments:** not reported	**Study inclusion criteria**: diagnosed with ILD (Idiopathic Pulmonary Fibrosis or Non Specific Interstitial Pneumonia) **Study exclusion criteria:** not reported **No. of participants enrolled:** 26 **No. of participants included in analysis:** assume 22 **No. completing study:** 22 **Reasons for withdrawals:** death 2; lost to follow-up 2.	**Outcome measures:** 6MWD Borg's dyspnoea scale **Methods of statistical analysis used:** assume study completers **Handling of missing data:** assume not included **Follow-up duration**: states post 12 weeks, no further details
Strookappe et al, 2015[39] **Country:** Netherlands **Language:** English **Source of funding:** non-commercial **Study design:** Before and After study (pilot study) **Number of centres:** one **Trial ID:** not reported **Objectives of study:** To establish whether patients suffering from pulmonary fibrosis might benefit from a physical training program.	**Intervention:** physical training programme, consisted of aerobic endurance training (stationary cycling, treadmill) and peripheral muscle strengthening. 24 sessions, each session 60 minutes and covered both components (more details provided). **Placebo or control:** not applicable **Duration:** 12 weeks **Modifications:** 6 participants used supplemental oxygen during the training programme. **Concurrent treatments:** not reported	**Study inclusion criteria:** none formally stated, participants were consecutive patients referred to the ILD out-patient clinic. Diagnoses were confirmed in accordance with accepted guidelines (ATS/ERS 1999; 2013). **Study exclusion criteria:** none **No. of participants enrolled:** 12 IPF (also 12 sarcoidosis, not extracted hereafter) **No. of participants included in analysis:** 12 **No. completing study:** 12 **Reasons for withdrawals:** not applicable	**Outcome measures ,** exercise capacity; 6MWT (using ATS guidelines); Borg Rating of Perceived Exertion (RPE) scale (range 6-20, no exertion to maximal exertion); Fatigue (Fatigue Assessment Scale; range 10-50, <22 no fatigue; ≥35 extreme fatigue); breathlessness intensity (modified Borg scale, score 0-7, higher score, greater breathlessness). **Methods of statistical analysis used**, all participants analysed **Handling of missing data:** no missing data **Follow-up duration:** 12 weeks (immediately after the end of the intervention)

Arizono et al, 2014[40] **Country:** Japan **Language:** English **Source of funding:** non-commercial **Study design:** prospective cohort study **Number of centres:** 1 **Trial ID:** not reported **Objectives of study:** to compare the responsiveness of 5 exercise measurements by evaluating the efficacy of pulmonary rehabilitation in subjects with IPF.	**Intervention:** Twice weekly 90 minute supervised exercise training covering respiratory care, education, endurance and strength training (total 20 sessions). If desaturation <80% during exercise supplemental oxygen was given. **Placebo or control:** control, no intervention (including pulmonary rehabilitation or new medicines) **Duration:** 10 weeks **Modifications:** not reported **Concurrent treatments:** pulmonary rehabilitation group: prednisolone n=3; prednisolone and cyclosporine n=3. Control group: prednisolone n=2; sildenafil n=1	**Study inclusion criteria**: < 75 years, IPF (ATS/ERS 2002), shortness of breath on effort, stable clinical condition with no infection or exacerbation prior 3 months **Study exclusion criteria:** severe comorbid illnesses, collagen vascular diseases, need for long-term oxygen therapy. **No. of participants enrolled:** total 53; pulmonary rehabilitation 26; control 27 **No. of participants included in analysis:** total 48; pulmonary rehabilitation 24; control 24 **No. completing study:** total 48; pulmonary rehabilitation 24; control 24 **Reasons for withdrawals:** pulmonary rehabilitation: exacerbation 1; long term oxygen therapy 1; control: exacerbation 1; long term oxygen therapy 1; recruited for another study 1	**Outcome measures:** 6MWT Modified Borg scale (dyspnoea) Incremental shuttle walk distance **Methods of statistical analysis used:** study completers **Handling of missing data:** not applicable **Follow-up duration**: 10 weeks
Gaunaurd et al, 2014[41-43] **Jackson et al, 2012[44]** Linked to Jackson et al 2014 that is included in the Cochrane review of PR. **Country:** USA **Language:** English **Source of funding:** non-commercial **Study design:** RCT (pilot) **Number of centres:** 1 **Trial ID:** NCT01118221 **Objectives of study:** to determine whether PR increased physical activity…and improved quality of life and symptoms…for IPF.	**Intervention:** pulmonary rehabilitation: 2 weekly 90-minute sessions with education and supervised aerobic and strengthening exercises, required to complete all 24 sessions. 10 educational lectures (topics presented listed). Supervised exercise included 30 min cardiopulmonary endurance training, 20 min flexibility exercises, and 25 min strength training (targeted goals stated) given by a physical therapist. Home exercise program twice a week on days when not dong the PR. **Placebo or control:** no organised exercise. Handouts from education given to PR group. **Duration:** 3 months **Modifications:** participants had different goals and progressed as tolerated.	**Study inclusion criteria**: presenting with IPF (ATS/ERS 2011 criteria) with onset between 3-48 months prior to screening, HRCT highly probable IPF, right ventricular systolic pressure ≤55 mmHg and no decompensated right heart failure, 40-80 years, abnormal pulmonary function tests, 6MWT ≥150m and ≤500m; worsening condition, no infection, neoplasm, sarcoidosis or collagen-vascular disease **Study exclusion criteria:** any other condition likely to result in death within 2 years, history of unstable or deteriorating cardiac or neurological disease, current treatment with corticosteroids, pregnancy or lactation, degenerative arthritis, stroke or other limitation to mobility, oxygen saturation on room air <80% at rest. **No. of participants enrolled:** total 25; PR 14; control 11 **No. of participants included in analysis:** total 21; PR 11; control 10	**Outcome measures:** 6MWD (primary outcome; no data in Gaunaurd, covered in Cochrane review of Jackson) Borg dyspnoea Index SGRQ-IPF (reported in Cochrane review but different data here, for symptoms scale only) **Methods of statistical analysis used:** completers **Handling of missing data:** not reported **Follow-up duration**: 6 months

	Concurrent treatments: supplemental oxygen in those receiving it before study enrolment.	**No. completing study:** total 21; PR 11; control 10 **Reasons for withdrawals:** PR 2 left study, 1 died; control 1 left study	
Rifaat et al, 2014[45, 46] **Country:** Egypt **Language:** English **Source of funding:** Not reported **Study design:** Before and after **Number of centres:** one **Trial ID:** Not reported **Objectives of study:** To evaluate the role of PR in improving the functional status and dyspnea scale in patients with IPF	**Intervention:** Pulmonary rehabilitation: upper and lower extremity exercises, breathing exercise, chest physical therapy (more details provided), psychological support and patient education (no further details). Three sessions per week. **Placebo or control:** not applicable **Duration:** 8 weeks **Modifications:** Not reported **Concurrent treatments:** Not reported	**Study inclusion criteria**: IPF diagnosis according to ATS/ERS/JRS/ALAT 2011 **Study exclusion criteria:** pulmonary fibrosis not due to IPF, IPF in exacerbation, severe comorbid illnesses, unable to walk unassisted for balance, need for long-term oxygen therapy **No. of participants enrolled:** 30 **No. of participants included in analysis:** 30 **No. completing study:** 30 **Reasons for withdrawals:** not applicable	**Outcome measures:** 6MWD, Modified Borg Scale (MBS, 0-10, none-very severe dyspnoea), SGRQ (symptoms, activity, and impact and sum total score, 0 to 100, lower score indicates better HRQL) **Methods of statistical analysis used:** all participants analysed **Handling of missing data:** assume no missing data **Follow-up duration**: 8 weeks (immediately after intervention)
Ryerson et al, 2014[47-50] **Country:** USA , Canada **Language:** English **Source of funding:** States none **Study design:** Before and after study **Number of centres:** 3 **Trial ID:** NCT01055730 **Objectives of study:** 1) To determine the short-term and long-term impact of PR on functional and symptomatic outcomes; 2) to define the baseline factors that predict functional change post-rehabilitation; and 3) to characterize the relationship of changes in QOL to changes in function and symptom scores	**Intervention:** PR. 3 programmes, all conformed to standard ATS/ERS recommendations. Twice-weekly sessions of supervised exercise, individually tailored according to level of functional impairment, severity of ILD, comorbid disease and any other factors that could limit exercise. Exercise prescription based on medical history, clinical findings and 6-MWT. Educational sessions including symptom control, use of oxygen, and disease self-management strategies. Attended a mean of 15 sessions (all enrolled patients, range 10-24). **Placebo or control:** N/A **Duration:** 6 to 9 weeks (average 7 weeks)	**Study inclusion criteria**: a diagnosis of ILD from their treating physician and referral to a participating pulmonary rehabilitation program. **Study exclusion criteria:** None reported. **No. of participants enrolled:** 54 (outcomes extracted for n=35 with IPF, NSIP, unclassifiable ILD) **No. of participants included in analysis:** 39 (32 of 35) **No. completing study:** 39 of 54 (31 of 35) **Reasons for withdrawals:** 4 died, 1 fall/pneumonia, 1 compression fracture, 8 lost, 1 moved (not reported for ILD participants separately)	**Outcome measures:** 6MWD, MCID of 28m (primary outcome) Functional status (4MWD, 4m walk speed) Rapid Assessment of Physical Activity questionnaire (RAPA), 7-point questionnaire SGRQ (MCID 5-8 points) UCSD SOBQ (MCID 5 points) Geriatric Depression Scale (GDS), MCID 1 point global assessment of overall change in exercise capacity (ability to walk) **Methods of statistical**

	Modifications: Not reported **Concurrent treatments:** Not reported		**analysis used:** Per protocol **Handling of missing data:** Not reported **Follow-up duration**: 6-months
Vainshelboim et al, 2014[51-53] Vainshelboim et al, 2013[54] Vainshelboim et al, 2015**[55]** Vainshelboim et al, 2016**[56]** Vainshelboim et al, 2017**[57]** **Country:** Israel **Language:** English **Source of funding:** not reported, appear to be some commercial funds **Study design:** RCT **Number of centres:** one **Trial ID:** NCT01499745 **Objectives of study:** to examine the effect of exercise training on clinical outcomes in IPF patients	**Intervention:** Exercise training (ET): twice weekly 60-minute supervised by clinical exercise physiologist, physiotherapist, respiratory nurse and study physician. Two 6-week progressive blocks. 1) aerobic interval training (details provided) of 5 minutes followed by 1 minute rest, for 5 repetitions. The duration of activity increased each session until reached 15 minutes continuous exercise. Thresholds of intensity stated. Also 5-8 minutes self-paced walking, 10 minutes of resistance training (details reported) and 5 minutes of flexibility training. 2) increased up to 20 minutes continuous aerobic endurance training, stair climbing for 3-5 minutes and load for resistance training increased. Education on symptom management and encouraged to do physical activity on non training days. Also 'continued' on an outpatient PR program. **Placebo or control:** regular medical care alone (permitted to receive pulmonary rehabilitation for 3-months, twice weekly sessions after 12 weeks). **Duration:** 12 weeks **Modifications:** not reported **Concurrent treatments:** 5 in ET group received supplemental oxygen during exercise sessions. 9 in the ET group and 13 in control group received corticosteroids. 1	**Study inclusion criteria**: IPF (ATS/ERS 2011), clinically stable for the previous 3–6 months **Study exclusion criteria:** severe comorbid illnesses, unstable cardiac disease, any neurological or orthopedic contraindications for ET, IPF exacerbation and participation in a PR program in the prior 12 months. **No. of participants enrolled:** total 34; ET 16; control 18 **No. of participants included in analysis:** immediately after intervention period and 30 month assessment: total 32; ET 15; control 17 At 11 month follow-up; total 14; ET 14; control 14 **No. completing study:** completed intervention: total 32; ET 15; control 17 **Reasons for withdrawals:** during 12 week intervention: ET: 1 acute IPF exacerbation, control: 1 withdrew consent. During follow-up to 11 months: ET 1 withdrew consent; control 1 withdrew consent, 2 died.	**Outcome measures:** 6MWD, co-primary outcome (included in Cochrane for 12 week assessment but data slightly different so extracted) Dyspnoea by NMRC scale, 0-4 scale (in Cochrane for 12 week assessment but data slightly different so extracted)) SGRQ (no data in Cochrane) Serious adverse events Survival Complications of IPF **Methods of statistical analysis used:** study completers **Handling of missing data:** not applicable **Follow-up duration**: Most outcomes 11 months. 30 months [median 22.7 months , 95% CI 19.2-23.1] (assessment of survival and hospitalisations)

	ET and 2 controls received pirfenidone. All patients encouraged to engage in physical activity, such as walking at their own pace for a total of 30 to 60 minutes daily		
Holland, 2012[58] + 2011[59] **Country:** Australia **Language:** English **Source of funding:** none **Study design:** before and after study **Number of centres:** two **Trial ID:** not reported **Objectives of study:** to establish the impact of the aetiology and severity of ILD on response to pulmonary rehabilitation	**Intervention:** twice-weekly exercise training programme of endurance and strength training according to a standardised protocol (reference to Holland 2008 RCT); unsupervised home exercise programme prescribed, aim 5 sessions per week; education and self-management programme. **Placebo or control:** not applicable **Duration:** 8 weeks (abstract says 7 weeks) **Modifications:** none reported **Concurrent treatments:** supplemental oxygen as required to maintain oxygen saturation at least 85% (in n=17)	**Study inclusion criteria**: documented ILD (for IPF 2000 ATS/ERS) ambulant and reported dyspnoea on exertion on stable medical therapy **Study exclusion criteria:** history of syncope on exertion; any comorbidities precluding exercise training; or participation in a pulmonary rehabilitation program in the last two years **No. of participants enrolled:** 44 (abstract says 43); IPF 25; other ILDs (most not relevant to this review) 19 **No. of participants included in analysis:** 42 immediately; 41 at 6 months **No. completing study:** 41 **Reasons for withdrawals:** 2 (with IPF) did not complete rehabilitation programme and withdrew from study, 1 died. An additional 4 did not complete	**Outcome measures:** 6MWD change (primary outcome), MID ≥34metres CRQ dyspnoea (primary endpoint), MID ≥ 2.5 points. Proportion of participants achieving gains exceeding the MID for 6MWD and CRQ dyspnoea **Methods of statistical analysis used:** states ITT but also reports that data were available for smaller numbers **Handling of missing data:** not described **Follow-up duration**: 6-months
Kozu et al, 2011[60] (overlap of patients with Kozu 2011 [61]) **Country:** Japan **Language:** English **Source of funding:** not reported **Study design:** Before and after study **Number of centres:** one **Trial ID:** not reported **Objectives of study:** to compare the outcomes of rehabilitation in patients with IPF, who were grouped according to the MRC dyspnoea scale	**Intervention:** Pulmonary rehabilitation. MRC grade 2-4: two 90 min sessions/ week of exercise training (endurance and strength training of upper and lower limbs), relaxation, breathing retraining (breathing control techniques to reduce respiratory frequency) and education (benefits and importance of exercise, energy conservation, self-management of exacerbations). Home exercise programme included walking and strength training, 4-5 days/week. Intensity and/or duration increased weekly. MRC grade 5: unsupervised home-based programme similar to above, 2 weekly supervise exercise by physiotherapist, 2 x week telephone contact.	**Study inclusion criteria**: IPF diagnosed according to ATS/ERS 2000, under care of a respiratory physician, ambulant, reported dyspnoea on exertion, clinically stable with no changes in medication for ≥ 4 weeks before recruitment. **Study exclusion criteria:** MRC dyspnoea grade 1, severe orthopaedic or neurological disorders limiting exercise performance, unstable cardiac disease, active cancer, inability to complete questionnaires, previous pulmonary rehabilitation. **No. of participants enrolled:** 65 **No. of participants included in analysis:** 65 **No. completing study:** 63 (however, 15 withdrew from the intervention) **Reasons for withdrawals:** 2 died (those not completing	**Outcome measures:** 6MWD (primary) SF-36 (primary) Dyspnoea, Borg category ratio scale Limitations in activities of daily living (ADL) (reference provided, higher score better) Hospitalisations Adverse events **Methods of statistical analysis used:** All enrolled patients **Handling of missing data:** LCOF

	Placebo or control: not applicable **Duration:** 8-weeks **Modifications:** Not reported **Concurrent treatments:** Not reported	the intervention; 6 exacerbations, 4 declined, 3 'other', 2 died)	**Follow-up duration**: 8 weeks (immediately after intervention)
Swigris et al, 2011[62, 63] **Country:** USA **Language:** English **Source of funding:** commercial and non-commercial **Study design:** Before and After study **Number of centres:** 1 **Trial ID:** none **Objectives of study: to evaluate the effect of pulmonary rehabilitation (PR) in IPF** and analyse changes in functional capacity, fatigue, anxiety, depression, sleep, and health status from baseline to after completion of a standard, PR program in IPF.	**Intervention:** The PR program consisted of 18 sessions over 6 to 8 weeks. In accordance with ATS standards, and based on the NETT PR program, the exercise component at each centre included aerobic (treadmill, stationary bike, or similar apparatus) and resistance (light weights, resistance bands, or machines) training; and instruction on breathing techniques (pursed-lipped, controlled, and diaphragmatic breathing), pacing, and energy conservation. Exercise regimens were individualised based on patient status and estimated ability. The aerobic component was begun at a level to achieve a heart rate 60% of predicted maximum for age; intensity and duration were gradually increased to build tolerance and confidence. **Placebo or control:** not applicable **Duration:** 6 weeks **Modifications:** not reported **Concurrent treatments:** During PR SPO_2 was monitored and oxygen flow titrated to ensure saturation > 89%.	**Study inclusion criteria**: diagnosis of IPF: no identifiable cause for lung fibrosis, and usual interstitial pneumonia lung injury confirmed by the characteristic pattern on high-resolution computed tomogram or via surgical lung biopsy; PR not completed within the last 2 years; ability to walk **Study exclusion criteria:** patients with conditions that precluded the safe completion of PR (e.g. unstable coronary artery disease). **No. of participants enrolled:** 22 **No. of participants included in analysis:** 14 **No. completing study:** 14 **Reasons for withdrawals:** Death from IPF exacerbation 2; did not enrol in PR 4; withdrew due to back pain 1; withdrew before baseline data collected 1.	**Outcome measures:** Functional capacity (6WMD) Fatigue (fatigue severity scale) Anxiety (GAD-7) Depression (PHQ-8) Sleep (Pittsburgh Sleep Quality Index) Health status (SF-36) **Methods of statistical analysis used:** completers **Handling of missing data:** not applicable **Follow-up duration**: 6 weeks
Ozalevli et al, 2010[64] **Country:** Turkey **Language:** English	**Intervention:** 12-week home-based PR program consisting of pursed-lips breathing, thoracic expansion exercises, diaphragmatic	**Study inclusion criteria**: IPF diagnosis according to ATS/ERS 2000 criteria; being clinically stable; treatment with no more than 20mg prednisone/day; not having any	**Outcome measures:** Dyspnea (MRC Scale), Pulmonary function

Source of funding: not reported **Study design:** Before and After study **Number of centres:** 1 **Trial ID:** none **Objectives of study:** to investigate the effects of a home-based pulmonary rehabilitation program on the functional outcome parameters in patients with IPF.	breathing exercises, upper and lower extremity exercises combined with breathing control (pectoral muscles stretch, trunk extension, bilateral shoulder elevation, sit-to-stand exercises using a chair) and a walking program (15-30 min/day). Breathing control training, coping strategies to deal with shortness of breath and relaxation training were provided. Patients were instructed to perform all exercises 5 days/week, in three sessions/day with 10 repeats. They were recommended to have a break and rest in the case of excessive fatigue and shortness of breath and to continue exercises according to their fatigue tolerance. Supervision of the program was by phone calls once a week and a daily exercise query. In order to increase patients' adherence to the program, a booklet was prepared and the instructions about the program were given to patients with this booklet. **Placebo or control**: not applicable **Duration:** 12 weeks **Modifications:** not reported **Concurrent treatments:** not reported	pulmonary infections such as pneumonia at least in the last 6 weeks; not having serious uncontrolled cardiological and psychological problems; not receiving supplementary oxygen therapy; having no neurological, inner ear or orthopaedic disease; being able to ambulate without assistance or assistive devices and willingness to participate in this study **Study exclusion criteria:** obstructive lung disease (FEV1/FVC < 80%) such as COPD or asthma; acute coronary artery disease; collagen vascular disease; pneumoconiosis; sarcoidosis; cancer; nonparenchymal restrictive lung disease; other severe comorbid conditions. Patients who did not perform the home-based PR program on a regular basis and those who voluntarily left the study were excluded. **No. of participants enrolled:** 17 **No. of participants included in analysis:** 15 **No. completing study:** 15 **Reasons for withdrawals:** Two patients failed to complete the required number of sessions because of infectious disease and were excluded from the study.	(pulmonary function test) Exercise capacity (6MWD) Qol (SF-36) **Methods of statistical analysis used:** completers **Handling of missing data:** not applicable **Follow-up duration**: 12 weeks
Rammaert et al, 2009[65, 66] **Country:** France **Language:** English **Source of funding:** not reported **Study design:** Before and After study **Number of centres:** 1 **Trial ID:** none **Objectives of study:** to evaluate	**Intervention:** 8-week home-based pulmonary rehabilitation program over 10 months. A member of the rehabilitation team provided personalised follow up to patients once a week for 90 minutes after training diagnostic assessment. Retraining program lasted 30 to 45 minutes a day and included endurance training, muscle strengthening exercises, activities of daily living, walking	**Study inclusion criteria**: IPF diagnosis according to ATS/ERS 2000 criteria, ability to perform a walk test and use a cycle ergometer, agreement to setting up a home-based rehabilitation program. **Study exclusion criteria:** contraindications to functional exercise testing, acute exacerbation of IPF, changes in therapy planned in the coming 8 weeks, patients not requiring O_2 therapy during exercise.	**Outcome measures:** Exercise capacity (6MWD and others) Pulmonary function (spirometry, DLCO and plethysmography) Dyspnea (Borg scale, MRC scale and BDI) Quality of life (SF-36, SGRQ,

the impact of an 8-week home-based pulmonary rehabilitation over 10 months in stable patients with IPF	and learning to climb stairs. Patients were encouraged to carry out daily exercise program independently. Compliance was assessed weekly. A patient education program was implemented with a picture folder and fact sheets **Placebo or control:** not applicable **Duration:** 8 weeks **Modifications:** not reported **Concurrent treatments:** oxygen therapy was prescribed during exercise to improve the physical performance of patients when SpO_2 measured during the 6-minute walk test was less than 90%.	**No. of participants enrolled:** 17 **No. of participants included in analysis:** 13 **No. completing study:** 14 **Reasons for withdrawals: three had exacerbation of fibrosis during the study (2 died) and 1 patient developed a gluteal abscess.**	VAS) HADS **Methods of statistical analysis used:** completers **Handling of missing data:** not applicable **Follow-up duration**: 10 months
Holland et al, 2008[67] **Country:** **Language:** English **Source of funding:** non-commercial **Study design:** RCT **Number of centres:** 2 **Trial ID:** NCT00168285 **Objectives of study:** to establish the safety of exercise training in ILD; its effects on exercise capacity, dyspnoea and quality of life; and whether patients with IPF had similar responses to those with other types of ILD.	**Intervention:** twice weekly exercise training programme for 8 weeks. The exercise prescription consisted of 30 min of endurance exercise at each session, comprising both stationary cycling and walking training. Upper limb endurance training and functional strength training for the lower limbs were performed. Exercise was monitored and progressed by an experienced physiotherapist according to a standardised protocol. Once established on a supervised exercise regimen, an unsupervised home exercise programme was prescribed with the aim of achieving five exercise sessions per week in total. **Placebo or control:** weekly telephone calls during the 8 week period to provide support and general health advice.	**Study inclusion criteria**: patients over 18 years with documented ILD of any aetiology. ILD diagnosis was according to established criteria. For IPF, diagnostic criteria were consistent with those outlined in the International Consensus Statement. Patients were ambulant and reported dyspnoea on exertion on stable medical therapy **Study exclusion criteria:** history of syncope on exertion or any comorbidities which precludes exercise training (such as severe orthopaedic or neurological deficits or unstable cardiac disease). Patients who participated in a pulmonary rehabilitation programme in the past 12 months **No. of participants enrolled:** total 57 (34 IPF); exercise training 30; control 27 **No. of participants included in analysis:** 57 (34 IPF) **No. completing study:** total 46; exercise training 25; control 21	**Outcome measures:** Primary outcome Functional exercise capacity Secondary outcomes Maximal exercise capacity QoL (assessed using the SF-36 and CRDQ) Dyspnoea (assessed using the mMRC scale) **Methods of statistical analysis used:** ITT **Handling of missing data:** Missing data were replaced by the last-observation carried-forward (LOCF) method **Follow-up duration**: 26

	Duration: 8 weeks for the intervention. However, patients were followed up for 26 weeks **Modifications:** not reported **Concurrent treatments:** supplemental oxygen was provided during training if necessary to achieve oxygen saturation >85%.	**Reasons for withdrawals:** exercise training group: IPF exacerbation (n = 1), unwell (n = 2), did not wish to complete (n = 3), declined (n = 5), deceased (n = 2). Control group: deceased (n = 3), declined (n = 1), unwell (n = 4)	weeks
Jastrzebski et al, 2008[68] **Country:** Poland **Language:** Polish **Source of funding:** unclear as full article not translated **Study design:** CCT **Number of centres:** unclear as full article not translated **Trial ID:** unclear as full article not translated **Objectives of study:** to analyse the influence of inspiratory muscle training on dyspnea (oxygen cost diagram [OCD], baseline dyspnea index [BDI]), quality of life (SF-36), results of 6 MWT (distance, dyspnea in Borg's scale), maximal inspiratory pressure (MIP), and lung function tests (IC, TLC, VC, FEV1, DLCOSB, DLCO/VA) in patients with IPF.	**Intervention:** 12 weeks of Inspiratory muscle training added to general body conditioning **Placebo or control:** General body conditioning **Duration:** 12 weeks **Modifications:** unclear as full article not translated **Concurrent treatments:** unclear as full article not translated	**Study inclusion criteria**: IPF diagnosed by ATS/ERS criteria in patients over 50 years, and by lung biopsy in patients < 50 years. At least 2 years duration of disease. Patients were in remission i.e. no infection or disease exacerbation requiring increased doses of corticosteroids in past month **Study exclusion criteria:** more than 20mg prednisone/day, duration of treatment > 2 years, use of home oxygen therapy **No. of participants enrolled:** total 30; 16 patients in intervention group and 14 in control group **No. of participants included in analysis:** 30 **No. completing study:** unclear as full article not translated **Reasons for withdrawals:** 4 eligible participants did not complete the study, 2 withdrew despite no side effects, 2 excluded due to exacerbations	**Outcome measures:** Dyspnoea (oxygen cost diagram [OCD]) Baseline dyspnea index (BDI) Quality of life (SF-36), 6MWT (distance, dyspnea in Borg's scale) Maximal inspiratory pressure (MIP) Lung function tests (IC, TLC, VC, FEV1, DLCOSB, DLCO/VA) **Methods of statistical analysis used:** unclear as full article not translated **Handling of missing data:** unclear as full article not translated **Follow-up duration**: 12 weeks
Nishiyama et al, 2008[69] **Country:** Japan **Language:** English **Source of funding:** non-commercial **Study design:** RCT **Number of centres:** 1	**Intervention:** The PR program was a 10-week general program and not one specifically for IPF. It involved a twice-a-week outpatient programme of exercise training integrated with peripheral muscle training. In the first week, baseline assessments were made and maximal	**Study inclusion criteria**: age less than 75 years; a diagnosis of IPF according to ATS/ERS 2000 criteria; shortness of breath on effort; and a stable clinical condition with no infection or exacerbation in the previous 3 months. **Study exclusion criteria:** severe comorbid illnesses,	**Outcome measures:** Pulmonary function Blood gas analysis 6MWD Dyspnea (BDI) HRQoL (SGRQ)

Trial ID: none **Objectives of study:** to evaluate the effects of pulmonary rehabilitation in IPF.	exercise tests on a cycle ergometer was also performed by some patients. From the 2nd to the 9th week, exercise training was performed on a treadmill at 80% of the patient's maximal walking speed. Strength training for the limbs was conducted using elastic bands; exercises included arm raising and knee extensions for about 20 min. Assessments were repeated in the final week to evaluate the effect of PR. Some educational lectures were held during the program. **Placebo or control:** usual care **Duration:** 10 weeks **Modifications:** not reported **Concurrent treatments:** Supplemental oxygen was given to maintain oxygen saturation above 90% if desaturation was observed.	collagen vascular diseases, the need for long-term oxygen therapy and previous treatment with corticosteroids or immunosuppressants. **No. of participants enrolled:** 30: 15 intervention and 15 control **No. of participants included in analysis:** 28 **No. completing study:** 28 **Reasons for withdrawals:** Two patients refused to participate in the PR program	**Methods of statistical analysis used:** completers **Handling of missing data:** not applicable **Follow-up duration**: 10 weeks
Case-conference			
Bajwah et al, 2015[70, 71] **Country:** UK **Language:** English **Source of funding:** Non-commercial **Study design:** RCT (feasibility) **Number of centres:** one **Trial ID:** NCT01450644 **Objectives of study:** To obtain preliminary information on the impact of a case conference intervention delivered in the home (Hospital2Home) on palliative care concerns of patients and their carers, and to evaluate feasibility	**Intervention:** Fast-track (received intervention after 1 week) to Hospital2Home, a case conference intervention involving a case conference (multiprofessional + holistic) and a care plan (care individualised to each patient + carer). Delivered by a palliative care specialist nurse location chosen by the patient. Median length of case conference 90 min. Current and anticipated care palliative care concerns, including physical, psychological, social and spiritual discussed. Where appropriate, end-of-life preferences discussed. **Placebo or control:** Waiting list (received	**Study inclusion criteria**: clinical diagnosis of advanced idiopathic fibrotic lung disease (IPF by ATS/ERS 2000 criteria or fibrotic non-specific interstitial pneumonia), ≥18 years **Study exclusion criteria:** none reported **No. of participants enrolled:** 53 (Fast-track 26, waiting list 27) **No. of participants included in analysis:** 47 (Fast-track 23, waiting list 24) **No. completing study:** 34 (Fast-track 19, waiting list 15) **Reasons for withdrawals:** Total 22	**Outcome measures:** Palliative Care Outcome Scale (POS, score 0-40, higher score indicated more severe) (primary); D12 scale (breathlessness at best/worse); Kings Brief Interstitial Lung Disease questionnaire (KBILD, increases indicate improvement) and SGRQ, MRC breathlessness scale. **Methods of statistical analysis used:** ITT analysis. **Handling of missing data:**

and acceptability	intervention after 4 weeks) **Duration:** single intervention **Modifications:** not applicable **Concurrent treatments:** All patients received best standard care, including input from ILD physicians, ILD clinical nurse specialist, occupational therapist, physiotherapist and oxygen assessment and treatment services. Access to inpatient ILD treatment and community health professionals as needed.	Fast track 7: withdrew 1, died 1, lost to follow-up 2, no return of questionnaire 3. Waiting list 15: died 9, lost to follow-up 1, no return of questionnaire 4, too unwell 1.	Only patients with week 4 data were included in change analysis. **Follow-up duration**: 4 weeks (and at 8 weeks – after wait list group had received intervention)
Disease Management Programme			
Lindell et al, 2010[72] **Country:** USA **Language:** English **Source of funding:** non-commercial **Study design:** RCT **Number of centres:** 1 **Trial ID:** not provided **Objectives of study:** to test the ability of the Program to Reduce Idiopathic Pulmonary Fibrosis Symptoms and Improve Management (PRISIM) to decrease symptom burden, decrease stress, and improve perceptions of HRQoL for patients with IPF and their care partner	**Intervention:** The PRISIM intervention consisted of 6 weekly group sessions attended by patients and care partners. The content for the sessions was developed collaboratively by a pulmonary clinical nurse specialist whose practice involved patients with IPF, a psychiatric clinical specialist with training as a cognitive behavioural therapist, and an advanced care planning instructor. The sessions reviewed the causes, pathophysiology, and treatment of IPF; basic principles of cognitive behaviour techniques and cognitive distortions; concepts of stress and depression and interrelationships with illness; planning for uncertainty and concerns related to terminal illness, communicating with clinicians, coping, and planning to one's affairs; symptom management, energy conservation, oxygen therapy, and the importance of exercise; on informal discussion and review. Each session lasted 2 hours. Both groups received a copy of the book Feeling Good: The New Mood	**Study inclusion criteria**: age > 21 years; ability to read and understand English; IPF diagnosis; and FVC reflecting moderate (FVC 55%–70% predicted) or severe (FVC < 55% predicted) disease. Care partners were required to be > 21 years; able to read and understand English; and to live with or care for the patient with IPF **Study exclusion criteria:** not reported **No. of participants enrolled:** total 42 (numbers added up to 41); PRISIM intervention 10 patients and 10 caregivers; control 11 patients and 10 caregivers **No. of participants included in analysis:** 37 **No. completing study:** 37 **Reasons for withdrawals:** Two dyads did not continue because the patient died or received a lung transplant. The third caregiver failed to return after randomisation. All were enrolled in the control group.	**Outcome measures:** Dyspnoea (UCSD) Anxiety (Beck Anxiety Inventory) Depression (Beck Depression Inventory-II) Stress (Perceived Stress scale) HRQoL (SF-36 version 2) **Methods of statistical analysis used:** completers **Handling of missing data:** not reported **Follow-up duration**: 6 weeks

	Therapy 39 to read at leisure (controls) or use in group exercises (experimental group) **Placebo or control:** Patients in usual care were seen by members of the clinical care team every 3 to 6 months. The pulmonary clinical nurse specialist was available by phone to answer questions and conducted a monthly support group for those wanting to attend. Psychologic counselling was provided, if indicated, but was not offered on a routine basis. **Duration:** 6 weeks **Modifications:** not reported **Concurrent treatments:** not reported		
Patient and Partner Empowerment Programme			
van Manen et al, 2017[73, 74] **Country:** The Netherlands **Language:** English **Source of funding:** None **Study design:** CCT **Number of centres:** one **Trial ID:** Not reported **Objectives of study:** to determine the effect of a short multidisciplinary empowerment programme on the QoL for patients with IPF and their partners.	**Intervention:** Patient and Partner Empowerment Programme (PPEPP). 3 meetings, focus on coping with IPF, also importance of exercise, breathing techniques, practical support, current treatments. Led by psychologist; pulmonologist, specialised ILD nurse, oxygen supplier, social worker and physiotherapists also contributed. Further details provided. **Placebo or control:** Control group offered opportunity to attend future PPEPP **Duration:** 3 weeks **Modifications:** Not reported **Concurrent treatments:** Not reported	**Study inclusion criteria**: diagnosed with IPF according ATS/ERS/JRS/ALAT guidelines 2011, life expectancy of ⩾1 year, lung function with FVC ⩾45% of predicted, DLCO ⩾25% of predicted. **Study exclusion criteria:** No additional criteria reported. **No. of participants enrolled:** total 23, PPEPP 15, control 8 (plus 23 partners) **No. of participants included in analysis:** total 20, PPEPP 13, control 7 **No. completing study:** total 20, PPEPP 13, control 7 **Reasons for withdrawals:** PPEPP: clinical worsening of IPF (1), influenza infection (1); control: died (1)	**Outcome measures:** not specified as primary or secondary. King's Brief Interstitial Lung Disease health status questionnaire (K-BILD, higher score better), Euroqol5D5L (EQ5D5L, higher score better), MRC dyspnoea scale (lower score better). Perceived Stress Scale (PSS) **Methods of statistical analysis used:** Completers **Handling of missing data:** Not reported **Follow-up duration**: 3 months

CCT: Controlled Clinical Trial; CRQ: Chronic Respiratory Questionnaire; ITT: Intention to Treat; MRC: Medical Research Council; PR: Pulmonary Rehabilitation; QoL: Quality of Life; RCT: Randomised Controlled Trial

References

1. Corte TJ, Keir GJ, Dimopoulos K, Howard L, Corris PA, Parfitt L, Foley C, Yanez-Lopez M, Babalis D, Marino P, Maher TM, Renzoni EA, Spencer L, Elliot CA, Birring SS, O'Reilly K, Gatzoulis MA, Wells AU, Wort SJ, Group BS. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *American Journal of Respiratory & Critical Care Medicine* 2014: 190(2): 208-217.

2. Keir G, Corte T, Parfitt L, Maher T, Marino P, Renzoni E, Dimopoulos K, Gatzoulis M, Madden B, Howard L, Corris P, O'Reilly K, Hope-Gill B, Birring S, Wells A, Wort SJ. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia: A randomized, double-blind, placebo-controlled study. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2013: 42(no pagination).
3. King TE, Jr., Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, Valeyre D, Leconte I, Morganti A, Roux S, Behr J. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *American Journal of Respiratory & Critical Care Medicine* 2011: 184(1): 92-99.
4. King TE, Jr., Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stahler G, Leconte I, Roux S, Raghu G. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008: 177(1): 75-81.
5. Jackson RM, Glassberg MK, Ramos CF, Bejarano PA, Butrous G, Gomez-Marin O. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. *Lung* 2010: 188(2): 115-123.
6. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010: 363(7): 620-628.
7. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest* 2007: 131(3): 897-899.
8. Zeng ZY. Recent study on traditional Chinese medicine foot bath combined with traditional Chinese and western medicine nursing for IPF. *Chinese community doctors [zhong guo she qu yi shi]* 2015: 31(14): 143-146.
9. Yu Y, Sun Z, Shi L, Zhang Y, Zhou Z, Zhang S, Chao E. Effects of Feiwei granules in the treatment of idiopathic pulmonary fibrosis: a randomized and placebo-controlled trial. *Journal of Traditional Chinese Medicine* 2016: 36(4): 427-433.
10. Nathan S, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez F, Corte T, Keogh A, Leuchte H, Mogulkoc N, Ulrich S, Wuyts W, Malcolm S, Shah S, Yao M, Wells A. RISE-IIP: Riociguat for the treatment of pulmonary hypertension associated with idiopathic interstitial pneumonia. *European Respiratory Journal* 2017: 50.
11. Hoeper MM, Halank M, Wilkens H, Gunther A, Weimann G, Gebert I, Leuchte HH, Behr J. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. *European Respiratory Journal* 2013: 41(4): 853-860.
12. Visca D, Mori L, Tsipouri V, Canu S, Bonini M, Pavitt M, Fleming S, Firouzi A, Farquhar M, Leung E, Hogben C, De Lauretis A, Kokosi M, Lee J, Lyne R, Rippon N, Chetta A, Russell AM, Saunders P, Kouranos V, Margaritopoulos G, Maher TM, Stockford A, Cullinan P, Hopkins N, Birring S, Wells AU, Whitty J, Banya W, Adamali H, Spencer L, Sestini P, Renzoni EA. Ambox: A Randomised Controlled, Crossover Trial Evaluating The Effects Of Ambulatory Oxygen On Health Status In Patients With Fibrotic Interstitial Lung Disease. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
13. Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, Mitchell RA, Sheel AW, Khalil N, Camp PG, et al. Effects of hyperoxia on dyspnoea and exercise endurance in fibrotic interstitial lung disease. *The european respiratory journal* 2017: 49(5).
14. Papiris SA, Kagouridis K, Kolilekas L, Papaioannou AI, Roussou A, Triantafillidou C, Baou K, Malagari K, Argentos S, Kotanidou A, Karakatsani A, Manali ED. Survival in Idiopathic pulmonary fibrosis acute exacerbations: the non-steroid approach. *BMC Pulmonary Medicine* 2015: 15: 162.
15. Fiorucci E, Lucantoni G, Paone G, Zotti M, Li BE, Serpilli M, Regimenti P, Cammarella I, Puglisi G, Schmid G. Colchicine, cyclophosphamide and prednisone in the treatment of mild-moderate idiopathic pulmonary fibrosis: comparison of three currently available therapeutic regimens. *Eur Rev Med Pharmacol Sci* 2008: 12(2): 105-111.

16. Hope-Gill BD, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003: 168(8): 995-1002.
17. Dutta P, Funston W, Mossop H, Ryan V, Jones R, Forbes R, Sen S, Pearson J, Griffin SM, Smith JA, Ward C, Forrest IA, Simpson AJ. Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. *Thorax* 2019.
18. Kilduff CE, Counter MJ, Thomas GA, Harrison NK, Hope-Gill BD. Effect of acid suppression therapy on gastroesophageal reflux and cough in idiopathic pulmonary fibrosis: an intervention study. *Cough (London, England)* 2014: 10: 4.
19. Horton MR, Santopietro V, Mathew L, et al. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: A randomized trial. *Annals of Internal Medicine* 2012: 157(6): 398-406.
20. Horton MR, Danoff SK, Lechtzin N. Thalidomide inhibits the intractable cough of idiopathic pulmonary fibrosis. *Thorax* 2008: 63: 749-749.
21. Birring S, Wijsenbeek M, Al SA, Tutuncu A, Morice A. Significant improvement in refractory chronic cough with inhaled PA101 in patients with idiopathic pulmonary fibrosis: Results from phase 2 trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
22. Birring SS, Wijsenbeek MS, Agrawal S, van den Berg JWK, Stone H, Maher TM, Tutuncu A, Morice AH. A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial. *Lancet Respir Med* 2017: 5(10): 806-815.
23. Satia I, Badri H, Dockry R, Chaudhuri N, Brown G, Abbott-Banner K, Smith JA. A randomised, double-blind, placebocontrolled crossover study to assess the efficacy of a single dose of 100 mg of VRP700 by inhalation in reducing the frequency and severity of cough in adult patients with idiopathic pulmonary fibrosis. *Thorax* 2015: 70: A52.
24. Allen S, Raut S, Woollard J, Vassallo M. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. *Palliative Medicine* 2005: 19(2): 128-130.
25. Chehere B, Bougault V, Chenivesse C, Grosbois J-M, Wallaert B. Cardiorespiratory adaptation in a 6-minute walk test by fibrotic idiopathic interstitial pneumonia patients who did or did not respond to pulmonary rehabilitation. *European journal of physical and rehabilitation medicine* 2018.
26. Nolan CM, Maddocks M, Maher TM, Patel S, Barker RE, Jones SE, Kwan H, Mehta B, Hogg L, Tuffnell R, George PM, Cullinan P, Man WD. Improvement in Gait Speed with Pulmonary Rehabilitation Is Associated with Increased Survival in Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2018: 197.
27. Del Castillo NT, Paredes L, Shek N, Gutierrez HH, Betancourt-Pena J. Benefits of Pulmonary Rehabilitation in Patients With Idiopathic Pulmonary Fibrosis and Other Interstitial Lung Diseases. *Chest* 2017: 152(4): 982A-982A.
28. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, Glaspole I, Goh NS, Southcott AM, Burge AT, Gillies R, Martin A, Holland AE. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax* 2017: 17.
29. Dowman L, McDonald CF, Hill C, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge A, Ndongo R, Martin A, Holland AE. The benefits of exercise training in interstitial lung disease: protocol for a multicentre randomised controlled trial. *BMC Pulmonary Medicine* 2013: 13: 8.
30. Dowman L, McDonald C, Hill C, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge A, Ndongo R, Martin A, Holland A. Effect of disease aetiology on response to exercise training in patients with interstitial lung disease. *Respirology* 2015: 20: 58.

31. Dowman LM, McDonald CF, Hill CJ, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge AT, Ndongo R, Martin A, Holland AE. 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: 191(no pagination).
32. Nolan CM, Maddocks M, Delogu V, Patel S, Barked RE, Mehta B, Hogg L, Tuffnell R, Canavan JL, Jonesi SE, Koni SS, Maher TM, Cullinan P, Man WD. Responsiveness And Minimum Clinically Important Difference (mcid) Of The 4 Metre Gait Speed (4mgs) In Fibrotic Interstitial Lung Disease. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
33. Jarosch I, Schneeberger T, Gloeckl R, Kreuter M, Neurohr C, Prasse A, Behr J, Kenn K. Effects of a 3-week pulmonary rehabilitation program in patients with idiopathic pulmonary fibrosis-a randomized, controlled trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
34. Schneeberger T, Glockl R, Jarosch I, Behr J, Neurohr C, Frankenberger M, Prasse A, Kreuter M, Kenn K. Effects of a 3-week inpatient pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis - a randomized, controlled trial. *Wiener Klinische Wochenschrift* 2016: 128(19-20): 779-780.
35. Jarosch I, Schneeberger T, Gloeckl R, Kreuter M, Benstz J, Frankenberger M, Neurohr C, Prasse A, Behr J, Kenn K. Different Effects Of Pulmonary Rehabilitation In Anxious Vs. Non-Anxious Patients With Idiopathic Pulmonary Fibrosis - A Pilot Study. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
36. Keyser RE, Woolstenhulme JG, Chin LM, Nathan SD, Weir NA, Connors G, Drinkard B, Lamberti J, Chan L. Cardiorespiratory function before and after aerobic exercise training in patients with interstitial lung disease. *Journal of Cardiopulmonary Rehabilitation & Prevention* 2015: 35(1): 47-55.
37. Keyser RE, Christensen EJ, Chin LM, Woolstenhulme JG, Drinkard B, Quinn A, Connors G, Weir NA, Nathan SD, Chan LE. Changes in fatigability following intense aerobic exercise training in patients with interstitial lung disease. *Respiratory Medicine* 2015: 109(4): 517-525.
38. Rastogi SA, Koltharkar M, Udwadia ZF. Prospective study of pulmonary rehabilitation in interstitial lung disease in resource limited setting: An Indian experience. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2015: 191(no pagination).
39. Strookappe B, Elfferich M, Swigris J, Verschoof A, Veschakelen J, Knevel T, Drent M. Benefits of physical training in patients with idiopathic or end-stage sarcoidosis-related pulmonary fibrosis: a pilot study. *Sarcoidosis Vasculitis & Diffuse Lung Diseases* 2015: 32(1): 43-52.
40. Arizono S, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, Ogawa T, Watanabe F, Nishiyama O, Nishimura K, Kozu R, Tabira K. Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis. *Respiratory Care* 2014: 59(7): 1108-1115.
41. Gaunaurd IA, Gomez-Marin OW, Ramos CF, Sol CM, Cohen MI, Cahalin LP, Cardenas DD, Jackson RM. Physical activity and quality of life improvements of patients with idiopathic pulmonary fibrosis completing a pulmonary rehabilitation program. *Respiratory Care* 2014: 59(12): 1872-1879.
42. Gaunaurd IA, Cardenas DD, Cahalin LP, Cohen MI, Ramos CF, Jackson RM. Health-related quality of life of IPF patients in a pulmonary rehabilitation program (Abstract). American Journal of Respiratory and Critical Care Medicine, 2014; p. A2639.
43. Gomez O, Ramos CF, Cardenas D, Gaunaurd I, Eustis N, Cohen M, Jackson RM. Exercise training during pulmonary rehabilitation increases activity levels of IPF patients. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2012: 185(no pagination).

44. Jackson R, Ramos C, Cardenas D, Sol C, Cohen M, Gaunaurd I. Effects of aerobic and strength training on symptoms and exercise capacity of IPF patients [Abstract]. European Respiratory Journal, 2012; p. 672s [P3686].
45. Rifaat N, Anwar E, Ali YM, Ellabban A, Hasan AA. Value of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Egyptian Journal of Chest Diseases and Tuberculosis* 2014: 63(4): 1013-1017.
46. 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: 44(no pagination).
47. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, Khalil N, Collard HR, Garvey C. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respiratory Medicine* 2014: 108(1): 203-210.
48. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp P, Wilcox PG, Khalil N, Garvey CM, Collard HR. Pulmonary rehabilitation improves long-term quality of life in patients with interstitial lung disease. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2013: 187(no pagination).
49. Ryerson CJ, Cayou C, Topp FJ, Hilling L, Wilcox PG, Khalil N, Collard HR, Garvey CM. Pulmonary rehabilitation in interstitial lung disease: Predictors of success. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2012: 185(no pagination).
50. Ryerson CJ, Topp F, Cayou C, Hilling L, Camp P, Khalil N, Wilcox PG, Collard HR, Garvey CM. A low baseline 6mwd predicts greater improvement from pulmonary rehabilitation in interstitial lung disease. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2013: 187(no pagination).
51. Vainshelboim B, Oliveira J, Yehoshua L, Weiss I, Fox BD, Fruchter O, Kramer MR. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. *Respiration* 2014: 88(5): 378-388.
52. Vainshelboim B, Oliveira J, Fox BD, Yehoshua L, Fruchter O, Kramer MR. Effect of exercise pulmonary rehabilitation on long-term outcomes in idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2014: 189(no pagination).
53. Vainshelboim B, Oliveira J, Fox B, Kramer M. Effect of exercise pulmonary rehabilitation on long-term outcomes in idiopathic pulmonary fibrosis. *European Respiratory Journal* 2014: 44(Suppl 58): P602.
54. Vainshelboim B, Oliveira J, Yohoshua L, Wais I, Kramer MR. Effect of Pulmonary Rehabilitation Program on Exercise Tolerance and Functional Capacity in Patients with Idiopathic Pulmonary Fibrosis. *Medicine and Science in Sports and Exercise* 2013: 45(5): 543-543.
55. 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): 345-354.
56. Vainshelboim B, Fox BD, Kramer MR, Izhakian S, Gershman E, Oliveira J. Short-Term Improvement in Physical Activity and Body Composition After Supervised Exercise Training Program in Idiopathic Pulmonary Fibrosis. *Archives of Physical Medicine & Rehabilitation* 2016: 97(5): 788-797.
57. Vainshelboim B, Kramer MR, Fox BD, Izhakian S, Sagie A, Oliveira J. Supervised exercise training improves exercise cardiovascular function in idiopathic pulmonary fibrosis. *European journal of physical & rehabilitation medicine* 2016: 19.

58. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. *Respiratory Medicine* 2012: 106(3): 429-435.
59. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Benefits of exercise training are related to disease severity in idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2011: 183(1 MeetingAbstracts).
60. 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): 1196-1202.
61. Kozu R, Senjyu H, Jenkins SC, 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.
62. Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, Wamboldt FS. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. *Respir Care* 2011: 56(6): 783-789.
63. Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, Wamboldt FS. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis.[Erratum appears in Respir Care. 2013 Apr;58(4):e51]. *Respiratory Care* 2011: 56(6): 783-789.
64. Ozalevli S, Karaali HK, Ilgin D, Ucan ES. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Multidisciplinary Respiratory Medicine* 2010: 5(1): 31-37.
65. Rammaert B, Leroy S, Cavestri B, Wallaert B, Grosbois JM. [Home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis]. *Rev Mal Respir* 2009: 26(3): 275-282.
66. Rammaert B, Leroy S, Cavestri B, Wallaert B, Grosbois JM. Home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis. *Revue des Maladies Respiratoires* 2011: 28(7): e52-57.
67. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax, 2008; pp. 549-554.
68. Jastrzebski D, Kozielski J, Zebrowska A. [Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis with inspiratory muscle training]. *Pneumonol Alergol Pol* 2008: 76(3): 131-141.
69. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S, Nishimura K, Taniguchi H. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008: 13(3): 394-399.
70. Bajwah S, Ross JR, Wells AU, Mohammed K, Oyebode C, Birring SS, Patel AS, Koffman J, Higginson IJ, Riley J. Palliative care for patients with advanced fibrotic lung disease: a randomised controlled phase II and feasibility trial of a community case conference intervention. *Thorax* 2015: 70(9): 830-839.
71. Bajwah S, Higginson IJ, Wells AU, Koffman J, Ross JR, Birring SS. Developing and evaluating a hospital2home palliative care service for patients with advanced progressive idiopathic fibrotic interstitial lung disease: Phase 0-II [Abstract]. Palliative medicine, 2012; p. 545.
72. Lindell KO, Olshansky E, Song M, Zullo TG, Gibson KF, Kaminski N, Hoffman LA. Impact of a disease-management program on symptom burden and health-related quality of life in patients with idiopathic pulmonary fibrosis and their care partners. *Heart & Lung* 2010: 39(4): 304-314.

73. van Manen MGJ, van 't Spiker A, Tak NC, Baars CT, Jongenotter SM, van Roon LR, Kraan J, Hoogsteden HC, Wijsenbeek MS. Patient and partner empowerment programme for idiopathic pulmonary fibrosis. *European Respiratory Journal* 2017: 49: 1601596 [https://doi.org/1601510.1601183/13993003.13901596-13992016].
74. Van Manen M, Van't Spijker A, Tak N, Baars C, Jongenotter S, Van Roon L, Kraan J, Wijsenbeek M. Patient and partner "empowerment" program in idiopathic pulmonary fibrosis (ppepp): Improving quality of life in patients and their partners. *Qjm* 2016: 109: S46.

Suppl 4: Baseline characteristics of include participants (previous review studies in blue)

Study	Age, mean (SD) except otherwise stated	Male (%)	ILD type (%) (how diagnosed)	% predicted FVC and DLCO[#] mean (SD)[b]	6MWD mean (SD)[c]
Bosentan					
Corte et al, 2014[1, 2]	66.4 (9.2)	67.5	IPF: 76.7 Fibrotic NSIP: 23.3 ATS/ERS 2002 criteria	FVC: 55.7 (19.8)	149.3 (99.6)
	66.9 (9.3)	75		FVC: 51.1 (24.0)	170.7 (97.0)
King et al, 2011[3]	63.8 (8.4)	72.7	IPF 100 ATS/ERS 2000	FVC: 74.9 (14.8)	NA
	63.2 (9.1)	63.6		FVC: 73.1 (15.3)	
King Jr et al, 2008 (BUILD 1)[4]/Raghu et al, 2010 (2nd paper BUILD 1)[5]	65.3 (8.4)	69	IPF 100 ATS/ERS2000/2002 criteria	FVC: 65.9 (10.5)	375 (92)
	65.1 (9.1)	75.9		FVC: 69.5 (12.6)	372 (74)
Sildenafil					
Jackson et al, 2010[6]	70 (12.1)	79	IPF 100 ATS/ERS 2002	FVC: 62.2 (16.7)	333.9 (68.8)
	71 (6.2)	80		FVC: 62.7 (10.3)	358.8 (72.2)
Zisman et al, 2010[7]	69.8 (8.7)	90.4	IPF 100[1]	FVC: 54.9 (14)	NA
	68.2 (9.3)	82.4		FVC: 58.7 (14.1)	NA
Collard et al, 2007[8]	72 (7)	57.1	IPF 100 ATS/ERS criteria 2000	FVC: 69.6 (18.4)	147.9 (141.6)
Chinese medicine					
Yu et al, 2016[9]	NR	64.6[a]	IPF: 100 Chinese Thoracic Society criteria 2002	NR	335 (136)
	NR	56.7[a]	IPF: 100 Chinese Thoracic Society criteria 2002	NR	396 (159)
Zeng et al, 2015[10]	NR	NR	IPF 100 NR	NR	NR
	NR	NR	IPF 100 NR	NR	NR
	NR	NR	IPF 100 NR	NR	NR
	NR	NR	IPF 100 NR	NR	NR
Riociguat					
Nathan et al, 2017[11]	68 (8)	68.5	IPF 74 NSIP 12 Other 14	FVC: 76.3 (19.1); DLCO: 32 (11.8)[*]	307 (80)

[1] IPF defined by consensus criteria; advanced stage defined as a diffusing capacity for carbon monoxide of < 35% of the predicted value.

	69 (8)	61	IPF 66 NSIP 19 Other 15	FVC: 74.3 (15.7); DLCO: 30.5 (10.9)*	324 (66)
Hoeper et al, 2013[12]	60.5 (range 33.0–80.0)	63.6	IPF 59.1 Criteria not reported	FVC: 67 (20)	316 (96)
Oxygen					
Visca et al, 2017[13, 14]	64.5 (1.1)	69	IPF 52 Criteria not reported	FVC: 73.3 (19.1)	NR
Schaeffer et al, 2017[15]	NR for IPF subgroup	NR for IPF subgroup	IPF: 55, Other 45 Criteria not reported	NR for IPF subgroup	NR for IPF subgroup
Corticosteroids					
Papiris et al, 2015[16]	Median 68 (range 52–82)	75	IPF100 ATS/ERS 2011 criteria	Median FVC: 65.1 (range 34.3–94)	NA
	Median 71.5 (range 52–80)	50	IPF 100	Median FVC: 53.15 (range 27.1–81.8)	NA
Fiorucci et al, 2008[17]	65 (2.3)	54.5	IPF 100 ATS/ERS2000/2002 criteria	NR	NR
	65.1 (2.7)	55.6			
	65.2 (3.2)	60			
Hope-Gill et al, 2003[18]	71.7	90	IPF 100 ATS/ERS 2002	FVC: 77.4	NA
	59.3	80		FVC: 103.6	
Proton pump inhibitors					
Dutta et al, 2019[19]	71.3 (6.7)	83	IPF 100[2]	FVC: 73.1 (17.1)	Median (IQR): 416.5 (296.5-485)
	71 (7.3)	73		FVC: 77.9 (17.6)	Median (IQR): 372.5 (307.6-450)
Kilduff et al, 2014[20]	65 (95% CI 60–71)	72.2	IPF 100 ATS/ERS 2002 criteria	FVC: 83.1 (95% CI 74.1-92.1)	NR
Thalidomide					
Horton et al, 2012[21]	67.6 (7.8)	78	IPF: 100 HRCT or surgical lung biopsy demonstrating UIP	FVC: 70.4 (13.7)	NA
Horton et al, 2008[22]	NR	NR	IPF: 100 ATS/ERS 2000	NR	NR
PA 101					
Birring et al, 2016[23, 24]	67	63	IPF 100- MDT consensus	FVC: 73	NR

[2] IPF considered the most likely diagnosis by the regional ILD MDT; cough; radiological features of honeycombing HRCT scanning; bibasal inspiratory crackles on auscultation and features of a restrictive ventilatory defect (VC) <90% predicted and/or transfer factor for carbon monoxide (TLco) <90% predicted).

VRP 700					
Satia et al, 2014[25]	69.8 (6.9)	40	IPF 100 Criteria not reported	FVC litres 1.86 (0.42)	NR
Opioids					
Allen et al, 2005[26]	86 (range 78-92)	27.3	IPF 100 ATS/ERS	NR	NR
Pulmonary rehabilitation/exercise testing					
Chehere et al, 2019[27, 28]	65 (9)	78.9	IPF: 63.2, Fibrotic NSIP: 36.8 ATS/ERS criteria 2002, 2013	FVC: 75 (13); DLCO: 40 (8)*	425 (57)
Nolan et al, 2018[29]	74 (7)	70	IPF: 100 Criteria not reported	FVC: 72.4 (21.8)	NR
Del Castillo et al, 2017[30]	NR	NR	IPF: 32.1, Other ILD: 67.9 NR	NR	NR
Dowman et al, 2017 [31-34]	70 (10)	66	IPF 100 ATS/ERS criteria 2011	FVC: 74 (18); DLCO: 50 (17)~	456 (126)
	73 (9)	69	IPF 100 ATS/ERS criteria 2011	FVC: 78 (19); DLCO: 49 (11)~	398 (166)
Nolan et al, 2017[35]	NR	NR	IPF: 82.7%, Fibrotic NSIP: 17.3% Criteria not reported	NR	NR
Jarosch et al, 2016[36-38]	68 (9)	76	IPF: 100 Criteria not reported	FVC: 73.5 (18.7)	414.4 (98.1)[b]
	65 (10)	81	IPF: 100 Criteria not reported	FVC: 72.1 (20.3)	390.0 (107.5)[b]
Keyser et al, 2015[39, 40]	57.0 (9.1)	31	IPF: 23, Fibrotic NSIP: 46, Others: 31 Criteria not reported	FVC: 52.9 (18); DLCO: 39.4 (15)*	433 (92.6)
Rastogi et al, 2015[41]	NR	38.5	IPF: 61.5, Fibrotic NSIP: 38.58 Criteria not reported	FVC: 49.84 (11.08)	340 (47.21)
Strookappe et al, 2015[42]	67.3 (11.3)	75	IPF 100 ATS/ERS criteria 1999, 2013	FVC: 77.0 (13.4); DLCO: 40.9 (12.6)*	305 (137)
Arizono et al, 2014[43]	69.4 (7.4)	66.7	IPF 100 ATS/ERS 2002 criteria	VC 70.8 (18.1); DLCO: 49.7 (15.9)~	477.7 (9.0)
	69.4 (6.6)	66.7	IPF 100 ATS/ERS 2002 criteria	VC 75.7 (16.0); DLCO: 47.7 (17.4)~	499.4 (66.6)
Jackson et al, 2014[44, 45]/Gaunaurd et al, 2014[46-48]	71 (6), n=11	85.7	IPF: 100 ATS/ERS criteria 2011	FVC: 60 (11), n=11 DLCO: 44 (11)*	361 (55), n=11

	66 (7), n=10	81.8	IPF: 100 ATS/ERS criteria 2011	FVC: 61 (14), n=10 DLCO: 43 (11)*	339 (109), n=10
Rifaat et al, 2014[49, 50]	54.4 (6.1)	26.7	IPF 100 ATS/ERS criteria 2011	FVC: 51.9 (13.6); DLCO: 62.2 (13.5)˜	281.8 (64.7)
Ryerson et al, 2014[51-54]	70.3 (9.1)	51.4	IPF: 62.9, Fibrotic NSIP: 14.3, Unclassified: 22.6 Criteria not reported	FVC: 65.3 (19.7)	349.6 (108.9)
Vainshelboim et al, 2014[55-61]	68.8 (6)	67	IPF: 100 ATS/ERS criteria 2011	FVC: 66.1 (14.8) DLCO: 48.6 (17.2)˜	471 (108)
	66 (9)	65	IPF: 100 ATS/ERS criteria 2011	FVC: 70.1 (17.4) DLCO: 53.2 (12.2)˜	513 (108)
Holland et al, 2012[62, 63]	IPF: 72.9 (6.8); other ILDs 68.1 (8.4)	NR	IPF: 56.8 Fibrotic NSIP: 6.8 Other 36.4 (see appendix) ATS/ERS criteria 2000	IPF: FVC 76.4 (20.3); IPF DLCO: 48.5 (19.1)˜ other ILDs: FVC 72.1 (23.6) other ILDs DLCO: 51.7 (19.3)˜	IPF: 370 (127); other ILDs 411 (96)
Kozu et al, 2011a[64] (overlap of patients with Kozu et al 2011b[65])	 65.4 (7.7) 67.8 (7.5) 68.1 (7.6) 68.7 (7.5)	 81.3 76.5 64.7 60	IPF 100 IPF 100 IPF 100 IPF 100 ATS/ERS criteria 2000	FVC DLCO 83 (11) 58 (20)˜ 67 (13) 35 (10)* 60 (16) 28 (12)* 51 (11) 21 (8)*	 439 (52) 330 (60) 201 (50) 157 (43)
Swigris et al, 2011[66]	NR	NR	IPF: 100 ATS/ERS 2000	NR	906 (111)
	64.8 (5.9)	NR	COPD: 100 Gold criteria	NR	1157 (46)
Ozalevli et al, 2010[67]	62.8 (8.5)	66.7	IPF: 100 IPF: ATS/ERS 2000	FVC: 71.6 (8.2) DLCO: 68 (32.3)˜	390.3
Rammaert et al, 2009[68]			IPF: 100 IPF:ATS/ERS 2000	DLCO: 32 (13)*	
Holland et al, 2008[69][a]	72.9 (7)	58.8	IPF: 100 ATS/ERS 2000	NA	354 (125)
	72.3 (8)	NR			
Jastrzebski et al, 2008[70]	56.5 (6.5)	63	IPF 100 ATS/ERS 2000/2002 (50 yrs and above) Lung biopsy (< 50 yrs)	FVC: 67.3 (14.3); DLCO: 39.5 (15.9)*	NR
	56.2 (7.2)	64		FVC: 69.2 (14.6); DLCO: 38.1 (18.9)*	
Nishiyama et al, 2008[71]	68.1 (8.9)	92.3	IPF: 100 ATS/ERS 2002	FVC: 66.1 (13.2); DLCO: 59.4 (16.7)˜	385 (116)
	64.5 (9.1)	60	IPF: 100 ATS/ERS 2002	FVC: 68.7 (19.5); DLCO: 48.6 (16.7)˜	476 (128)

Case conference					
Bajwah et al, 2015[72, 73]	67.1 (10.9)	77	IPF: 85, Fibrotic NSIP: 15 ATS/ERS criteria 2000	NR	NR
	70.6 (10.3)	67	IPF: 82, Fibrotic NSIP: 18 ATS/ERS criteria 2000	NR	NR
Disease Management programme					
Lindell et al, 2010[74]	Patients: 65.2 (10.3) Care partners:63.3 (12.7)	Patients: 33.3 Care partners: 19	IPF: 100 Diagnosis Unclear	FVC > 55%: 8; 50 – 55%: 1; < 50%: 1	NR
	Patients: 67.1 (11.9) Care partners: 67 (8.6)	Patients:42.9 Care partner: 4.8		FVC > 55%: 6; 50 – 55%: 2; < 50%: 2	
Patient and Partner Empowerment Programme					
van Manen et al, 2017[75, 76]	Median 63 (range 54-74)	77	IPF 100 ATS/ERS criteria 2011	Median FVC: 80 (range 50-100)	NR
	Median 76 (range 63–82)	100	IPF 100 ATS/ERS criteria 2011	Median FVC: 78 (range 53–96)	NR

ATS/ERS: American Thoracic Society/ European Respiratory Society; CCT: Controlled Clinical Trial; DLCO: Diffusion Capacity of the Lung for Carbon monoxide; FVC: Forced vital capacity; ILD: Interstitial Lung Disease; IPF: Idiopathic pulmonary fibrosis; NR: not reported; NSIP: non specific interstitial pneumonia; PPEP: Patient and Partner Empowerment Programme; RCT: randomised controlled trial; RoB: risk of selection bias; SD: Standard Deviation; UIP: Usual Interstitial Pneumonia, VC vital capacity, HRCT- High-resolution chest computed tomography

[a]data from study author, [#]where DLCO, % pred < 45 disease was considered to be severe, [b]unless otherwise specified, *shows studies where patients had severe disease among studies on pulmonary rehabilitation/exercise training while ~ shows studies where patients did not have severe disease

References

1. Corte TJ, Keir GJ, Dimopoulos K, Howard L, Corris PA, Parfitt L, Foley C, Yanez-Lopez M, Babalis D, Marino P, Maher TM, Renzoni EA, Spencer L, Elliot CA, Birring SS, O'Reilly K, Gatzoulis MA, Wells AU, Wort SJ, Group BS. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *American Journal of Respiratory & Critical Care Medicine* 2014: 190(2): 208-217.
2. Keir G, Corte T, Parfitt L, Maher T, Marino P, Renzoni E, Dimopoulos K, Gatzoulis M, Madden B, Howard L, Corris P, O'Reilly K, Hope-Gill B, Birring S, Wells A, Wort SJ. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia: A randomized, double-blind, placebo-controlled study. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2013: 42(no pagination).
3. King TE, Jr., Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, Valeyre D, Leconte I, Morganti A, Roux S, Behr J. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *American Journal of Respiratory & Critical Care Medicine* 2011: 184(1): 92-99.
4. King TE, Jr., Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stahler G, Leconte I, Roux S, Raghu G. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008: 177(1): 75-81.
5. Raghu G, King TE, Jr., 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): 118-123.
6. Jackson RM, Glassberg MK, Ramos CF, Bejarano PA, Butrous G, Gomez-Marin O. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. *Lung* 2010: 188(2): 115-123.
7. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010: 363(7): 620-628.
8. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest* 2007: 131(3): 897-899.
9. Yu Y, Sun Z, Shi L, Zhang Y, Zhou Z, Zhang S, Chao E. Effects of Feiwei granules in the treatment of idiopathic pulmonary fibrosis: a randomized and placebo-controlled trial. *Journal of Traditional Chinese Medicine* 2016: 36(4): 427-433.
10. Zeng ZY. Recent study on traditional Chinese medicine foot bath combined with traditional Chinese and western medicine nursing for IPF. *Chinese community doctors [zhong guo she qu yi shi]* 2015: 31(14): 143-146.
11. Nathan S, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez F, Corte T, Keogh A, Leuchte H, Mogulkoc N, Ulrich S, Wuyts W, Malcolm S, Shah S, Yao M, Wells A. RISE-IIP: Riociguat for the treatment of pulmonary hypertension associated with idiopathic interstitial pneumonia. *European Respiratory Journal* 2017: 50.
12. Hoeper MM, Halank M, Wilkens H, Gunther A, Weimann G, Gebert I, Leuchte HH, Behr J. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. *European Respiratory Journal* 2013: 41(4): 853-860.
13. Visca D, Mori L, Tsipouri V, Canu S, Bonini M, Pavitt M, Fleming S, Firouzi A, Farquhar M, Leung E, Hogben C, De Lauretis A, Kokosi M, Lee J, Lyne R, Rippon N, Chetta A, Russell AM, Saunders P, Kouranos V, Margaritopoulos G, Maher TM, Stockford A, Cullinan P, Hopkins N, Birring S, Wells AU, Whitty J, Banya W, Adamali H, Spencer L, Sestini P, Renzoni EA. Ambox: A Randomised Controlled, Crossover Trial Evaluating The Effects Of Ambulatory Oxygen On Health Status In Patients With Fibrotic Interstitial Lung Disease. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
14. Visca D, Mori L, Tsipouri V, Fleming S, Firouzi A, Bonini M, Pavitt MJ, Alfieri V, Canu S, Bonifazi M, et al. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. *The lancet respiratory medicine* 2018: 6(10): 759-770.

15. Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, Mitchell RA, Sheel AW, Khalil N, Camp PG, et al. Effects of hyperoxia on dyspnoea and exercise endurance in fibrotic interstitial lung disease. *The european respiratory journal* 2017: 49(5).
16. Papiris SA, Kagouridis K, Kolilekas L, Papaioannou AI, Roussou A, Triantafillidou C, Baou K, Malagari K, Argentos S, Kotanidou A, Karakatsani A, Manali ED. Survival in Idiopathic pulmonary fibrosis acute exacerbations: the non-steroid approach. *BMC Pulmonary Medicine* 2015: 15: 162.
17. Fiorucci E, Lucantoni G, Paone G, Zotti M, Li BE, Serpilli M, Regimenti P, Cammarella I, Puglisi G, Schmid G. Colchicine, cyclophosphamide and prednisone in the treatment of mild-moderate idiopathic pulmonary fibrosis: comparison of three currently available therapeutic regimens. *Eur Rev Med Pharmacol Sci* 2008: 12(2): 105-111.
18. Hope-Gill BD, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003: 168(8): 995-1002.
19. Dutta P, Funston W, Mossop H, Ryan V, Jones R, Forbes R, Sen S, Pearson J, Griffin SM, Smith JA, Ward C, Forrest IA, Simpson AJ. Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. *Thorax* 2019.
20. Kilduff CE, Counter MJ, Thomas GA, Harrison NK, Hope-Gill BD. Effect of acid suppression therapy on gastroesophageal reflux and cough in idiopathic pulmonary fibrosis: an intervention study. *Cough (London, England)* 2014: 10: 4.
21. Horton MR, Santopietro V, Mathew L, et al. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: A randomized trial. *Annals of Internal Medicine* 2012: 157(6): 398-406.
22. Horton MR, Danoff SK, Lechtzin N. Thalidomide inhibits the intractable cough of idiopathic pulmonary fibrosis. *Thorax* 2008: 63: 749-749.
23. Birring S, Wijsenbeek M, Al SA, Tutuncu A, Morice A. Significant improvement in refractory chronic cough with inhaled PA101 in patients with idiopathic pulmonary fibrosis: Results from phase 2 trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
24. Birring SS, Wijsenbeek MS, Agrawal S, van den Berg JWK, Stone H, Maher TM, Tutuncu A, Morice AH. A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial. *The Lancet Respiratory Medicine* 2017: 08: 08.
25. Satia I, Badri H, Dockry R, Chaudhuri N, Brown G, Abbott-Banner K, Smith JA. A randomised, double-blind, placebocontrolled crossover study to assess the efficacy of a single dose of 100 mg of VRP700 by inhalation in reducing the frequency and severity of cough in adult patients with idiopathic pulmonary fibrosis. *Thorax* 2015: 70: A52.
26. Allen S, Raut S, Woollard J, Vassallo M. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. *Palliat Med* 2005: 19(2): 128-130.
27. Chehere B, Bougault V, Chenivesse C, Grosbois J-M, Wallaert B. Cardiorespiratory adaptation in a 6-minute walk test by fibrotic idiopathic interstitial pneumonia patients who did or did not respond to pulmonary rehabilitation. *European journal of physical and rehabilitation medicine* 2018.
28. Chehere B, Bougault V, Chenivesse C, Grosbois JM, Wallaert B. Cardiorespiratory adaptation during 6-Minute Walk Test in fibrotic idiopathic interstitial pneumonia patients who did or did not respond to pulmonary rehabilitation. *Eur J Phys Rehabil Med* 2019: 55(1): 103-112.
29. Nolan CM, Maddocks M, Maher TM, Patel S, Barker RE, Jones SE, Kwan H, Mehta B, Hogg L, Tuffnell R, George PM, Cullinan P, Man WD. Improvement in Gait Speed with Pulmonary Rehabilitation Is Associated with Increased Survival in Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2018: 197.
30. Del Castillo NT, Paredes L, Shek N, Gutierrez HH, Betancourt-Pena J. Benefits of Pulmonary Rehabilitation in Patients With Idiopathic Pulmonary Fibrosis and Other Interstitial Lung Diseases. *Chest* 2017: 152(4): 982A-982A.

31. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, Glaspole I, Goh NS, Southcott AM, Burge AT, Gillies R, Martin A, Holland AE. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax* 2017: 17.
32. Dowman L, McDonald CF, Hill C, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge A, Ndongo R, Martin A, Holland AE. The benefits of exercise training in interstitial lung disease: protocol for a multicentre randomised controlled trial. *BMC Pulmonary Medicine* 2013: 13: 8.
33. Dowman L, McDonald C, Hill C, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge A, Ndongo R, Martin A, Holland A. Effect of disease aetiology on response to exercise training in patients with interstitial lung disease. *Respirology* 2015: 20: 58.
34. Dowman LM, McDonald CF, Hill CJ, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge AT, Ndongo R, Martin A, Holland AE. 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: 191(no pagination).
35. Nolan CM, Maddocks M, Delogu V, Patel S, Barked RE, Mehta B, Hogg L, Tuffnell R, Canavan JL, Jonesi SE, Koni SS, Maher TM, Cullinan P, Man WD. Responsiveness And Minimum Clinically Important Difference (mcid) Of The 4 Metre Gait Speed (4mgs) In Fibrotic Interstitial Lung Disease. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
36. Jarosch I, Schneeberger T, Gloeckl R, Kreuter M, Neurohr C, Prasse A, Behr J, Kenn K. Effects of a 3-week pulmonary rehabilitation program in patients with idiopathic pulmonary fibrosis-a randomized, controlled trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
37. Jarosch I, Schneeberger T, Gloeckl R, Kreuter M, Benstz J, Frankenberger M, Neurohr C, Prasse A, Behr J, Kenn K. Different Effects Of Pulmonary Rehabilitation In Anxious Vs. Non-Anxious Patients With Idiopathic Pulmonary Fibrosis - A Pilot Study. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
38. Schneeberger T, Glockl R, Jarosch I, Behr J, Neurohr C, Frankenberger M, Prasse A, Kreuter M, Kenn K. Effects of a 3-week inpatient pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis - a randomized, controlled trial. *Wiener Klinische Wochenschrift* 2016: 128(19-20): 779-780.
39. Keyser RE, Christensen EJ, Chin LM, Woolstenhulme JG, Drinkard B, Quinn A, Connors G, Weir NA, Nathan SD, Chan LE. Changes in fatigability following intense aerobic exercise training in patients with interstitial lung disease. *Respiratory Medicine* 2015: 109(4): 517-525.
40. Keyser RE, Woolstenhulme JG, Chin LM, Nathan SD, Weir NA, Connors G, Drinkard B, Lamberti J, Chan L. Cardiorespiratory function before and after aerobic exercise training in patients with interstitial lung disease. *J Cardiopulm Rehabil Prev* 2015: 35(1): 47-55.
41. Rastogi SA, Koltharkar M, Udwadia ZF. Prospective study of pulmonary rehabilitation in interstitial lung disease in resource limited setting: An Indian experience. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2015: 191(no pagination).
42. Strookappe B, Elfferich M, Swigris J, Verschoof A, Veschakelen J, Knevel T, Drent M. Benefits of physical training in patients with idiopathic or end-stage sarcoidosis-related pulmonary fibrosis: a pilot study. *Sarcoidosis Vasculitis & Diffuse Lung Diseases* 2015: 32(1): 43-52.
43. Arizono S, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, Ogawa T, Watanabe F, Nishiyama O, Nishimura K, Kozu R, Tabira K. Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis. *Respiratory Care* 2014: 59(7): 1108-1115.
44. Jackson RM, Gomez-Marin OW, Ramos CF, Sol CM, Cohen MI, Gaunaurd IA, Cahalin LP, Cardenas DD. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. *Lung* 2014: 192(3): 367-376.

45. Jackson R, Ramos C, Cardenas D, Sol C, Cohen M, Gaunaurd I. Effects of aerobic and strength training on symptoms and exercise capacity of IPF patients [Abstract]. European Respiratory Journal, 2012; p. 672s [P3686].
46. Gaunaurd IA, Gomez-Marin OW, Ramos CF, Sol CM, Cohen MI, Cahalin LP, Cardenas DD, Jackson RM. Physical activity and quality of life improvements of patients with idiopathic pulmonary fibrosis completing a pulmonary rehabilitation program. *Respiratory Care* 2014: 59(12): 1872-1879.
47. Gaunaurd IA, Cardenas DD, Cahalin LP, Cohen MI, Ramos CF, Jackson RM. Health-related quality of life of IPF patients in a pulmonary rehabilitation program (Abstract). American Journal of Respiratory and Critical Care Medicine, 2014; p. A2639.
48. Gomez O, Ramos CF, Cardenas D, Gaunaurd I, Eustis N, Cohen M, Jackson RM. Exercise training during pulmonary rehabilitation increases activity levels of IPF patients. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2012: 185(no pagination).
49. Rifaat N, Anwar E, Ali YM, Ellabban A, Hasan AA. Value of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Egyptian Journal of Chest Diseases and Tuberculosis* 2014: 63(4): 1013-1017.
50. 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: 44(no pagination).
51. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, Khalil N, Collard HR, Garvey C. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respiratory Medicine* 2014: 108(1): 203-210.
52. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp P, Wilcox PG, Khalil N, Garvey CM, Collard HR. Pulmonary rehabilitation improves long-term quality of life in patients with interstitial lung disease. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2013: 187(no pagination).
53. Ryerson CJ, Cayou C, Topp FJ, Hilling L, Wilcox PG, Khalil N, Collard HR, Garvey CM. Pulmonary rehabilitation in interstitial lung disease: Predictors of success. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2012: 185(no pagination).
54. Ryerson CJ, Topp F, Cayou C, Hilling L, Camp P, Khalil N, Wilcox PG, Collard HR, Garvey CM. A low baseline 6mwd predicts greater improvement from pulmonary rehabilitation in interstitial lung disease. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2013: 187(no pagination).
55. Vainshelboim B, Oliveira J, Yehoshua L, Weiss I, Fox BD, Fruchter O, Kramer MR. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. *Respiration* 2014: 88(5): 378-388.
56. Vainshelboim B, Oliveira J, Fox B, Kramer M. Effect of exercise pulmonary rehabilitation on long-term outcomes in idiopathic pulmonary fibrosis. European respiratory journal, 2014.
57. Vainshelboim B, Oliveira J, Fox BD, Yehoshua L, Fruchter O, Kramer MR. Effect of exercise pulmonary rehabilitation on long-term outcomes in idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2014: 189(no pagination).
58. Vainshelboim B, Oliveira J, Yohoshua L, Wais I, Kramer MR. Effect of Pulmonary Rehabilitation Program on Exercise Tolerance and Functional Capacity in Patients with Idiopathic Pulmonary Fibrosis. *Medicine and Science in Sports and Exercise* 2013: 45(5): 543-543.
59. 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): 345-354.
60. Vainshelboim B, Fox BD, Kramer MR, Izhakian S, Gershman E, Oliveira J. Short-Term Improvement in Physical Activity and Body Composition After Supervised Exercise Training Program

in Idiopathic Pulmonary Fibrosis. *Archives of Physical Medicine & Rehabilitation* 2016: 97(5): 788-797.
61. Vainshelboim B, Kramer MR, Fox BD, Izhakian S, Sagie A, Oliveira J. Supervised exercise training improves exercise cardiovascular function in idiopathic pulmonary fibrosis. *European journal of physical & rehabilitation medicine* 2016: 19.
62. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. *Respiratory Medicine* 2012: 106(3): 429-435.
63. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Benefits of exercise training are related to disease severity in idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2011: 183(1 MeetingAbstracts).
64. 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): 1196-1202.
65. Kozu R, Senjyu H, Jenkins SC, 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.
66. Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, Wamboldt FS. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. *Respir Care* 2011: 56(6): 783-789.
67. Ozalevli S, Karaali HK, Ilgin D, Ucan ES. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Multidisciplinary Respiratory Medicine* 2010: 5(1): 31-37.
68. Rammaert B, Leroy S, Cavestri B, Wallaert B, Grosbois JM. [Home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis]. *Rev Mal Respir* 2009: 26(3): 275-282.
69. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax, 2008; pp. 549-554.
70. Jastrzebski D, Kozielski J, Zebrowska A. [Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis with inspiratory muscle training]. *Pneumonologia i alergologia polska* 2008: 76(3): 131-141.
71. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S, Nishimura K, Taniguchi H. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008: 13(3): 394-399.
72. Bajwah S, Ross JR, Wells AU, Mohammed K, Oyebode C, Birring SS, Patel AS, Koffman J, Higginson IJ, Riley J. Palliative care for patients with advanced fibrotic lung disease: a randomised controlled phase II and feasibility trial of a community case conference intervention. *Thorax* 2015: 70(9): 830-839.
73. Bajwah S, Higginson IJ, Wells AU, Koffman J, Ross JR, Birring SS. Developing and evaluating a hospital2home palliative care service for patients with advanced progressive idiopathic fibrotic interstitial lung disease: Phase 0-II [Abstract]. Palliative medicine, 2012; p. 545.
74. Lindell KO, Olshansky E, Song M, Zullo TG, Gibson KF, Kaminski N, Hoffman LA. Impact of a disease-management program on symptom burden and health-related quality of life in patients with idiopathic pulmonary fibrosis and their care partners. *Heart & Lung* 2010: 39(4): 304-314.
75. van Manen MGJ, van 't Spiker A, Tak NC, Baars CT, Jongenotter SM, van Roon LR, Kraan J, Hoogsteden HC, Wijsenbeek MS. Patient and partner empowerment programme for idiopathic pulmonary fibrosis. *European Respiratory Journal* 2017: 49: 1601596 [https://doi.org/1601510.1601183/13993003.13901596-13992016].
76. Van Manen M, Van't Spijker A, Tak N, Baars C, Jongenotter S, Van Roon L, Kraan J, Wijsenbeek M. Patient and partner "empowerment" program in idiopathic pulmonary fibrosis (ppepp): Improving quality of life in patients and their partners. *Qjm* 2016: 109: S46.

Suppl 5 Summary of quality assessment of included studies

RCTs and CCTs

Study Reference Intervention	Random sequence	Allocation concealment	Blinding participants and personnel (objective / subjective)	Blinding outcome assessors (objective / subjective)	Incomplete outcome data (objective / subjective)	Selective reporting	Other bias
Corte et al, 2014[1] Bosentan RCT	Unclear	Unclear	Unclear / Unclear	Unclear / Unclear	High / High	Low	Low
King et al, 2011[2] Bosentan RCT	Low	Low	Low / Low	Low / Low	Low / Low	Low	Low
King et al, 2008[3]/Raghu et al 2010 (2nd paper BUILD 1)[4] Bosentan RCT	Unclear	Unclear	Low / Low	Low / Low	Low / Low	Low	Low
Jackson et al, 2010[5] Sildenafil RCT	Unclear	Unclear	Low / Low	Low / Low	Low / Low	Low	Low
Zisman et al, 2010[6] Sildenafil RCT	Unclear	Unclear	Low / Low	Low / Low	Low / Low	High	High
Yu et al, 2016[7] Feiwei granules (Chinese medicine) RCT	Unclear	Unclear	Unclear / Unclear	Unclear / Unclear	High / High	Unclear	Unclear
Zeng et al, 2015[8] Traditional Chinese medicine RCT	Unclear	Unclear	Unclear / Unclear	Unclear / Unclear	Unclear / Unclear	Unclear	Unclear
Nathan et al, 2017[9] Riociguat RCT	Unclear	Unclear	Unclear/Unclear	Unclear/Unclear	High/High	Unclear	Unclear
Visca et al, 2017[10] Ambulatory oxygen. RCT	Unclear	Unclear	NA / High	NA / Unclear	NA / Unclear	High	Low
Schaeffer et al, 2017[11] Oxygen RCT (cross over)	Unclear	Unclear	Low/Low	High/High	Unclear/Unclear	Low	Unclear
Hope-Gill et al, 2003[12] Corticosteroids CCT	High	High	High / High	High / High	Low / Low	Low	High
Dutta et al, 2019[13] Proton pump inhibitor RCT	Low	Low	Low/Low	Low/Low	Low/Low	Low	Low
Horton et al, 2012[14] Thalidomide RCT	Low	Low	NA/Low	NA/Low	NA/Low	Low	Unclear
Birring et al, 2016[15] PA101 RCT	Low	Unclear	NA / Low	NA / Low	NA / Low	Low	Unclear
Satia et al, 2014[16] VRP700 RCT	Unclear	Unclear	Unclear / NA	Unclear / NA	Unclear / NA	Unclear	Unclear
Dowman et al, 2017 [17] Pulmonary rehabilitation RCT	Low	Low	High / High	Low / Low	Low / Low	Unclear	Low
Jarosch et al, 2016[18] Pulmonary rehabilitation RCT	Low	Low	High / High	Low / Low	Unclear / Unclear	Unclear	Low
Gaunaurd et al, 2014[19]/Jackson et al, 2012[20] Pulmonary rehabilitation RCT	Low	Unclear	NA / High	NA / High	NA / High	Low	Low
Vainshelboim et al, 2014[21]	Unclear	Unclear	High / High	High / High	Unclear / Unclear	High	Low

Pulmonary rehabilitation RCT							
Holland et al, 2008 Pulmonary rehabilitation RCT	Low	Low	High/High	Low/Low	Low/Low	Low/Low	Low
Jastrzebski et al, 2008 Pulmonary rehabilitation CCT	High	High	Unclear/Unclear	Unclear/Unclear	Unclear/Unclear	High	Unclear
Nishiyama et al, 2008[22] Pulmonary rehabilitation RCT	Low	Low	Unclear / Unclear	Unclear / Unclear	Unclear / Unclear	Unclear	Low
Bajwah et al, 2015[23] Case conference RCT	Low	Low	NA / High	NA / High	N/A / High	Low	Low
Lindell et al, 2010[24] Disease management programme RCT	Low	Unclear	Unclear / Unclear	Unclear / Unclear	High/High	Unclear	Low
van Manen et al, 2017[25, 26] Empowerment CCT	High	High	NA / High	NA / High	NA / Low	Unclear	Unclear

NA: not applicable

In assessing study quality, we used the Cochrane risk of bias (ROB) tool for RCTs and controlled clinical trials, with the risk of selection bias (i.e random sequence generation and allocation concealment) used to establish the overall risk of bias for each study. Where both random sequence generation and allocation concealment were rated low, the study was given a 'low' RoB; where either random sequence generation or allocation concealment was rated unclear, the study was given an unclear RoB; where both random sequence generation and allocation concealment were rated high, the study was given a 'high' RoB.

Before and After Studies (items 1-10)

Criteria	**Collard et al, 2007[27]** Sildenafil	**Hoeper et al, 2013[28]** Riociguat	**Fiorucci et al, 2008[29]** Corticosteroids	**Kilduff et al, 2014[30]** Proton Pump Inhibitor	**Horton et al, 2008[31]** Thalidomide	**Allen et al, 2005[32]** Opioids
1. Study question clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
2. Eligibility/selection criteria clearly described?	Yes	Yes	Yes	Yes	No	Yes
3. Participants representative?	CD	CD	CD	CD	CD	CD
4. All eligible participants enrolled?	CD	CD	No	Yes	CD	CD
5. Sample size sufficiently large?	CD	No	CD	No	CD	CD
6. Intervention clearly described and delivered consistently?	Yes	Yes	Yes	No	Yes	Yes
7. Outcome measures prespecified, defined, valid, reliable, assessed consistently?	Yes	Yes	Yes	Yes	Yes	Yes
8. Outcome assessors blinded?	No	No	No	No	No	No
9. Loss to follow-up ≤ 20% and losses accounted for in analysis?	No	No	CD	No	Yes	NA
10. Pre-post changes measured? Statistical tests?	Yes	Yes	Yes	Yes	Yes	Yes
Overall quality assessment	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**

CD: cannot determine; NA not applicable

For before and after studies, where three items or less were rated positively, a rating of 'poor' was given; where four to seven items were rated positively, a rating of 'fair' was given; where eight items or more were rated positively, a rating of 'good' was given.

Before and After Studies cont.1 (items 1-10)

Criteria	**Chehere et al, 2019[33]** Pulmonary rehabilitation	**Nolan et al, 2018[34]** Pulmonary rehabilitation	**Del Castillo et al, 2017[35]** Pulmonary rehabilitation	**Nolan et al, 2017[36]** Pulmonary rehabilitation	**Keyser et al, 2015[37]** Pulmonary rehabilitation
1. Study question clearly stated?	Yes	Yes	No	Yes	Yes
2. Eligibility/selection criteria clearly described?	Yes	No	No	No	Yes
3. Participants representative?	CD	CD	CD	CD	CD
4. All eligible participants enrolled?	No	CD	CD	CD	CD
5. Sample size sufficiently large?	CD	CD	CD	CD	No
6. Intervention clearly described and delivered consistently?	Yes	No	CD	No	Yes
7. Outcome measures prespecified, defined, valid, reliable, assessed consistently?	Yes	Yes	Yes	Yes	Yes
8. Outcome assessors blinded?	CD	CD	CD	CD	No
9. Loss to follow-up ≤ 20% and losses accounted for in analysis?	No	CD	CD	CD	No
10. Pre-post changes measured? Statistical tests?	Yes	Yes	Yes	Yes	Yes
Overall quality assessment	**Fair**	**Poor**	**Poor**	**Poor**	**Fair**

CD: cannot determine; NA not applicable

For before and after studies, where three items or less were rated positively, a rating of 'poor' was given; where four to seven items were rated positively, a rating of 'fair' was given; where eight items or more were rated positively, a rating of 'good' was given.

Before and After studies, cont.2 (items 1-10)

Criteria	**Rastogi et al, 2015[38]** Pulmonary rehabilitation	**Strookappe et al, 2015[39]** Pulmonary rehabilitation	**Rifaat et al, 2014[40]** Pulmonary rehabilitation	**Ryerson et al, 2014[41]** Pulmonary rehabilitation	**Holland, 2012[42]** Pulmonary rehabilitation	**Kozu et al, 2011[43]** Pulmonary rehabilitation
1. Study question clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
2. Eligibility/selection criteria clearly described?	No	No	Yes	Yes	Yes	Yes
3. Participants representative?	CD	Yes	CD	CD	CD	CD
4. All eligible participants enrolled?	CD	CD	CD	CD	Yes	Yes
5. Sample size sufficiently large?	No	No	Yes	Yes	Yes	No
6. Intervention clearly described and delivered consistently?	Yes	Yes	Yes	Yes	Yes	No
7. Outcome measures prespecified, defined, valid, reliable, assessed consistently?	Yes	Yes	Yes	Yes	Yes	Yes
8. Outcome assessors blinded?	No	No	No	No	No	No
9. Loss to follow-up ≤ 20% and losses accounted for in analysis?	Yes	Yes	Yes	No	Yes	No
10. Pre-post changes measured? Statistical tests?	Yes	Yes	Yes	Yes	Yes	Yes

Overall quality assessment	**Fair**	**Fair**	**Fair**	**Fair**	**Good**	**Fair**

CD: cannot determine

For before and after studies, where three items or less were rated positively, a rating of 'poor' was given; where four to seven items were rated positively, a rating of 'fair' was given; where eight items or more were rated positively, a rating of 'good' was given

Before and After studies, cont. 2 (items 1-10)

Criteria	**Swigris et al, 2011[44]** Pulmonary rehabilitation	**Ozalevli et al, 2010[45]** Pulmonary rehabilitation	**Rammaert et al, 2009[46]** Pulmonary rehabilitation
1. Study question clearly stated?	Yes	Yes	Yes
2. Eligibility/selection criteria clearly described?	Yes	Yes	Yes
3. Participants representative?	CD	CD	CD
4. All eligible participants enrolled?	CD	CD	CD
5. Sample size sufficiently large?	CD	CD	CD
6. Intervention clearly described and delivered consistently?	Yes	Yes	Yes
7. Outcome measures prespecified, defined, valid, reliable, assessed consistently?	Yes	Yes	Yes
8. Outcome assessors blinded?	No	No	No
9. Loss to follow-up ≤ 20% and losses accounted for in analysis?	No	No	No
10. Pre-post changes measured? Statistical tests?	Yes	Yes	Yes
Overall quality assessment	**Fair**	**Fair**	**Fair**

Cohort / Cross sectional studies

Criteria	**Papiris et al 2015[47]** Corticosteroids	**Arizono et al, 2014[48]** Pulmonary rehabilitation
1. Research question clearly stated?	Yes	Yes
2. Study population specified and defined?	Yes	Yes
3. Participation rate ≥ 50%?	CD	CD
4. Recruitment from similar populations? Eligibility criteria prespecified and applied uniformly?	CD	Yes
5. Sample size justification?	No	No
6. Exposure(s) measured prior to outcome(s) measured?	No	Yes
7. Timeframe sufficient?	CD	CD
8. Different levels of the examined?	No	No
9. Exposure measures defined, valid, reliable, implemented consistently?	CD	CD
10. Exposure(s) assessed more than once over time?	No	No
11. Outcome measures defined, valid, reliable, implemented consistently?	CD	Yes
12. Outcome assessors blinded?	No	No
13. Loss to follow-up ≤20%?	NA	Yes
14. Confounding variables measured and adjusted for?	No	No
Overall quality	**Poor**	**Poor**

CD: cannot determine; NA not applicable

For cross sectional/cohort studies, where six items or less were rated positively, a rating of 'poor' was given.

References

1. Corte TJ, Keir GJ, Dimopoulos K, Howard L, Corris PA, Parfitt L, Foley C, Yanez-Lopez M, Babalis D, Marino P, Maher TM, Renzoni EA, Spencer L, Elliot CA, Birring SS, O'Reilly K, Gatzoulis MA, Wells AU, Wort SJ, Group BS. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *American Journal of Respiratory & Critical Care Medicine* 2014: 190(2): 208-217.
2. King TE, Jr., Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, Valeyre D, Leconte I, Morganti A, Roux S, Behr J. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *American Journal of Respiratory & Critical Care Medicine* 2011: 184(1): 92-99.
3. King TE, Jr., Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stahler G, Leconte I, Roux S, Raghu G. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008: 177(1): 75-81.

4. Raghu G, King TE, Jr., 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): 118-123.
5. Jackson RM, Glassberg MK, Ramos CF, Bejarano PA, Butrous G, Gomez-Marin O. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. *Lung* 2010: 188(2): 115-123.
6. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010: 363(7): 620-628.
7. Yu Y, Sun Z, Shi L, Zhang Y, Zhou Z, Zhang S, Chao E. Effects of Feiwei granules in the treatment of idiopathic pulmonary fibrosis: a randomized and placebo-controlled trial. *Journal of Traditional Chinese Medicine* 2016: 36(4): 427-433.
8. Zeng ZY. Recent study on traditional Chinese medicine foot bath combined with traditional Chinese and western medicine nursing for IPF. *Chinese community doctors [zhong guo she qu yi shi]* 2015: 31(14): 143-146.
9. Nathan S, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez F, Corte T, Keogh A, Leuchte H, Mogulkoc N, Ulrich S, Wuyts W, Malcolm S, Shah S, Yao M, Wells A. RISE-IIP: Riociguat for the treatment of pulmonary hypertension associated with idiopathic interstitial pneumonia. *European Respiratory Journal* 2017: 50.
10. Visca D, Mori L, Tsipouri V, Canu S, Bonini M, Pavitt M, Fleming S, Firouzi A, Farquhar M, Leung E, Hogben C, De Lauretis A, Kokosi M, Lee J, Lyne R, Rippon N, Chetta A, Russell AM, Saunders P, Kouranos V, Margaritopoulos G, Maher TM, Stockford A, Cullinan P, Hopkins N, Birring S, Wells AU, Whitty J, Banya W, Adamali H, Spencer L, Sestini P, Renzoni EA. Ambox: A Randomised Controlled, Crossover Trial Evaluating The Effects Of Ambulatory Oxygen On Health Status In Patients With Fibrotic Interstitial Lung Disease. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
11. Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, Mitchell RA, Sheel AW, Khalil N, Camp PG, et al. Effects of hyperoxia on dyspnoea and exercise endurance in fibrotic interstitial lung disease. *The european respiratory journal* 2017: 49(5).
12. Hope-Gill BD, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003: 168(8): 995-1002.
13. Dutta P, Funston W, Mossop H, Ryan V, Jones R, Forbes R, Sen S, Pearson J, Griffin SM, Smith JA, Ward C, Forrest IA, Simpson AJ. Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. *Thorax* 2019.
14. Horton MR, Santopietro V, Mathew L, et al. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: A randomized trial. *Annals of Internal Medicine* 2012: 157(6): 398-406.
15. Birring S, Wijsenbeek M, Al SA, Tutuncu A, Morice A. Significant improvement in refractory chronic cough with inhaled PA101 in patients with idiopathic pulmonary fibrosis: Results from phase 2 trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
16. Satia I, Badri H, Dockry R, Chaudhuri N, Brown G, Abbott-Banner K, Smith JA. A randomised, double-blind, placebocontrolled crossover study to assess the efficacy of a single dose of 100 mg of VRP700 by inhalation in reducing the frequency and severity of cough in adult patients with idiopathic pulmonary fibrosis. *Thorax* 2015: 70: A52.
17. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, Glaspole I, Goh NS, Southcott AM, Burge AT, Gillies R, Martin A, Holland AE. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax* 2017: 17.

18. Jarosch I, Schneeberger T, Gloeckl R, Kreuter M, Neurohr C, Prasse A, Behr J, Kenn K. Effects of a 3-week pulmonary rehabilitation program in patients with idiopathic pulmonary fibrosis-a randomized, controlled trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
19. Gaunaurd IA, Gomez-Marin OW, Ramos CF, Sol CM, Cohen MI, Cahalin LP, Cardenas DD, Jackson RM. Physical activity and quality of life improvements of patients with idiopathic pulmonary fibrosis completing a pulmonary rehabilitation program. *Respiratory Care* 2014: 59(12): 1872-1879.
20. Jackson RM, Ramos CF, Cardenas D, Gaunaurd I, Eustis N, Cohen M, Gomez-Marin O. Effects of aerobic and strength training on symptoms and exercise capacity of IFP patients. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2012: 185(no pagination).
21. Vainshelboim B, Oliveira J, Yehoshua L, Weiss I, Fox BD, Fruchter O, Kramer MR. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. *Respiration* 2014: 88(5): 378-388.
22. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S, Nishimura K, Taniguchi H. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008: 13(3): 394-399.
23. Bajwah S, Ross JR, Wells AU, Mohammed K, Oyebode C, Birring SS, Patel AS, Koffman J, Higginson IJ, Riley J. Palliative care for patients with advanced fibrotic lung disease: a randomised controlled phase II and feasibility trial of a community case conference intervention. *Thorax* 2015: 70(9): 830-839.
24. Lindell KO, Olshansky E, Song M, Zullo TG, Gibson KF, Kaminski N, Hoffman LA. Impact of a disease-management program on symptom burden and health-related quality of life in patients with idiopathic pulmonary fibrosis and their care partners. *Heart & Lung* 2010: 39(4): 304-314.
25. van Manen MGJ, van 't Spiker A, Tak NC, Baars CT, Jongenotter SM, van Roon LR, Kraan J, Hoogsteden HC, Wijsenbeek MS. Patient and partner empowerment programme for idiopathic pulmonary fibrosis. *European Respiratory Journal* 2017: 49: 1601596 [https://doi.org/1601510.1601183/13993003.13901596-13992016].
26. Van Manen M, Van't Spijker A, Tak N, Baars C, Jongenotter S, Van Roon L, Kraan J, Wijsenbeek M. Patient and partner "empowerment" program in idiopathic pulmonary fibrosis (ppepp): Improving quality of life in patients and their partners. *Qjm* 2016: 109: S46.
27. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest* 2007: 131(3): 897-899.
28. Hoeper MM, Halank M, Wilkens H, Gunther A, Weimann G, Gebert I, Leuchte HH, Behr J. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. *European Respiratory Journal* 2013: 41(4): 853-860.
29. Fiorucci E, Lucantoni G, Paone G, Zotti M, Li BE, Serpilli M, Regimenti P, Cammarella I, Puglisi G, Schmid G. Colchicine, cyclophosphamide and prednisone in the treatment of mild-moderate idiopathic pulmonary fibrosis: comparison of three currently available therapeutic regimens. *Eur Rev Med Pharmacol Sci* 2008: 12(2): 105-111.
30. Kilduff CE, Counter MJ, Thomas GA, Harrison NK, Hope-Gill BD. Effect of acid suppression therapy on gastroesophageal reflux and cough in idiopathic pulmonary fibrosis: an intervention study. *Cough (London, England)* 2014: 10: 4.
31. Horton MR, Danoff SK, Lechtzin N. Thalidomide inhibits the intractable cough of idiopathic pulmonary fibrosis. *Thorax* 2008: 63: 749-749.
32. Allen S, Raut S, Woollard J, Vassallo M. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. *Palliative Medicine* 2005: 19(2): 128-130.

33. Chehere B, Bougault V, Chenivesse C, Grosbois J-M, Wallaert B. Cardiorespiratory adaptation in a 6-minute walk test by fibrotic idiopathic interstitial pneumonia patients who did or did not respond to pulmonary rehabilitation. *European journal of physical and rehabilitation medicine* 2018.
34. Nolan CM, Maddocks M, Maher TM, Patel S, Barker RE, Jones SE, Kwan H, Mehta B, Hogg L, Tuffnell R, George PM, Cullinan P, Man WD. Improvement in Gait Speed with Pulmonary Rehabilitation Is Associated with Increased Survival in Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2018: 197.
35. Del Castillo NT, Paredes L, Shek N, Gutierrez HH, Betancourt-Pena J. Benefits of Pulmonary Rehabilitation in Patients With Idiopathic Pulmonary Fibrosis and Other Interstitial Lung Diseases. *Chest* 2017: 152(4): 982A-982A.
36. Nolan CM, Maddocks M, Delogu V, Patel S, Barked RE, Mehta B, Hogg L, Tuffnell R, Canavan JL, Jonesi SE, Koni SS, Maher TM, Cullinan P, Man WD. Responsiveness And Minimum Clinically Important Difference (mcid) Of The 4 Metre Gait Speed (4mgs) In Fibrotic Interstitial Lung Disease. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
37. Keyser RE, Woolstenhulme JG, Chin LM, Nathan SD, Weir NA, Connors G, Drinkard B, Lamberti J, Chan L. Cardiorespiratory function before and after aerobic exercise training in patients with interstitial lung disease. *Journal of Cardiopulmonary Rehabilitation & Prevention* 2015: 35(1): 47-55.
38. Rastogi SA, Koltharkar M, Udwadia ZF. Prospective study of pulmonary rehabilitation in interstitial lung disease in resource limited setting: An Indian experience. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2015: 191(no pagination).
39. Strookappe B, Elfferich M, Swigris J, Verschoof A, Veschakelen J, Knevel T, Drent M. Benefits of physical training in patients with idiopathic or end-stage sarcoidosis-related pulmonary fibrosis: a pilot study. *Sarcoidosis Vasculitis & Diffuse Lung Diseases* 2015: 32(1): 43-52.
40. Rifaat N, Anwar E, Ali YM, Ellabban A, Hasan AA. Value of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Egyptian Journal of Chest Diseases and Tuberculosis* 2014: 63(4): 1013-1017.
41. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, Khalil N, Collard HR, Garvey C. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respiratory Medicine* 2014: 108(1): 203-210.
42. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. *Respiratory Medicine* 2012: 106(3): 429-435.
43. 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): 1196-1202.
44. Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, Wamboldt FS. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. *Respir Care* 2011: 56(6): 783-789.
45. Ozalevli S, Karaali HK, Ilgin D, Ucan ES. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Multidisciplinary Respiratory Medicine* 2010: 5(1): 31-37.
46. Rammaert B, Leroy S, Cavestri B, Wallaert B, Grosbois JM. [Home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis]. *Rev Mal Respir* 2009: 26(3): 275-282.
47. Papiris SA, Kagouridis K, Kolilekas L, Papaioannou AI, Roussou A, Triantafillidou C, Baou K, Malagari K, Argentos S, Kotanidou A, Karakatsani A, Manali ED. Survival in Idiopathic pulmonary fibrosis acute exacerbations: the non-steroid approach. *BMC Pulmonary Medicine* 2015: 15: 162.

48. Arizono S, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, Ogawa T, Watanabe F, Nishiyama O, Nishimura K, Kozu R, Tabira K. Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis. *Respiratory Care* 2014: 59(7): 1108-1115.

Suppl 6: Detailed results- effect sizes and pooled estimates where applicable
(previous review findings in blue)

Study	Outcomes assessed	Type of intervention		Difference between periods (95% CI), p-value or both
Bosentan				
Corte et al, 2014[1] [2]		Bosentan, n=40	Placebo, n=20	P-value
	6MWD, metre Change value from baseline at 16 weeks	-25.9 (56.7)	-53.1 (66.9)	0.42
	Total CAMPHOR score Change value from baseline at 16 weeks	1.41 (9.28)	1.57 (8.46)	0.69
	CAMPHOR symptoms score Change value from baseline at 16 weeks	0.0 (4.51)	0.43 (3.5)	0.92
King et al 2011[3]	SF-36 Physical functioning	Bosentan, n=407	Placebo, n=209	Effect size mean difference (95% CI) 0 [-3.9, 3.9]
	SF-36 Role-physical			-2.80 [-7.70, 2.20]
	SF-36 Pain Index			0.70 [-4.20, 5.70]
	SF-36 General health perception			-2.90 [-6.50, 0.60]
	SF-36 Vitality			-1.60 [-5.40, 2.10]
	SF-36 Social Functioning			-1.50 [-6.40, 3.40]
	SF36 Role-emotional			-3.20 [-8.60, 2.20]
	SF-36 Mental Health index			-1.60 [-5.30, 2.20]
	SF-36 Health transition score			0 [-0.20, 0.20]
	EuroQol EQ-5D Health state score			-0.04 [-0.10, 0.03]
	EuroQol EQ-5D Visual Analogue score			-1.50 [-5.40, 2.40]
	Transition dyspnoea Index			0.10 [-0.50, 0.70]
King Jr et al, 2008[4]	6MWD			Effect size mean difference (95%CI) -18.00 [-57.23, 21.23]
	SGRQ total			-6.60[-0.72, -12.48]
Sildenafil				
	6MWD			
Zisman et al 2010[5]	6MWD, Change value from baseline 95% CI	Sildenafil/Sildenafil, n = 89 - 28.52 (- 43.24, - 13.80)	Placebo/Sildenafil, n=91 - 45.22 (- 59.65, - 30.79)	16.7[-3.92, 37.32]
Jackson et al 2010[6]	6MWD	Sildenafil, n=14	Placebo, n=15	0.70[-0.43, 1.83]
	6MWD Pooled effect	Random effects meta-analysis 5.25 [-8.90 to 19.40], I^2=56.6%, p=0.47		
	Borg			
Zisman et al 2010[5]	Borg, Change value from baseline 95% CI	Sildenafil/Sildenafil, n = 89 0.04 (−0.30 to 0.37)	Placebo/Sildenafil, n=91 0.37 (0.04 to 0.70)	-0.34 [-0.81, 0.14]
Jackson et al 2010[6]	Borg	Sildenafil, n=14	Placebo, n=15	-31.0 [-77.73, 15.73]
	Borg Pooled effect	Fixed effects meta-analysis -0.34 [-0.82 to 0.13], I^2=39.5%, p=0.16		
Zisman et al 2010[5]	UCSD, Change value from baseline 95% CI	Sildenafil/Sildenafil, n = 89 0.22 (−3.10 to 3.54)	Placebo/Sildenafil, n=91 6.81 (3.53 to 10.08)	-6.58 [-11.25,-1.92]
	SGRQ total score, Change value from baseline 95% CI	−1.64 (−3.91 to 0.64)	2.45 (0.17 to 4.72)	-4.08 [-7.3, -0.86]
	SGRQ symptom score, Change value from baseline 95% CI	−3.58 (−7.02 to −0.13)	2.15 (−1.30 to 5.61)	-5.73[-10.61,-0.85]
	SGRQ activity score, Change value from baseline 95% CI	−1.15 (−3.68 to 1.38)	2.49 (0.00 to 4.99)	-3.64 [-7.2,-0.09]

	SGRQ impact score, Change value from baseline 95% CI	−0.88 (−3.78 to 2.02)	2.82 (−0.03 to 5.67)	-3.7[-7.76,0.37]
	SF36 aggregate physical score, Change value from baseline 95% CI	−0.51 (−1.86 to 0.83)	−0.35 (−1.68 to 0.99) −	-0.17 [-2.06,1.73]
	SF36 aggregate mental score, Change value from baseline 95% CI	1.30 (−0.59 to 3.18)	3.02 (1.15 to 4.89)	-1.72 [-4.38, 0.94]
	SF36 aggregate bodily pain score, Change value from baseline 95% CI	−0.21 (−2.13 to 1.71)	1.97 (0.08 to 3.85)	-2.17 [-4.86, 0.52]
	SF36 general health score, Change value from baseline 95% CI	−1.04 (−2.52 to 0.44)	−3.89 (−5.37 to −2.42)	2.86 [0.76, 4.95]
	SF36 mental health score, Change value from baseline 95% CI	−0.16 (−1.81 to 1.49)	−1.31 (−2.93 to 0.30)	1.15 [-1.15, 3.46]
	SF36 physical functioning, Change value from baseline 95% CI	−0.93 (−2.24 to 0.38)	−1.46 (−2.76 to −0.17)	0.53[-1.31, 2.37]
	SF36 role emotional score, Change value from baseline 95% CI	−2.72 (−5.56 to 0.12)	−4.82 (−7.63 to −2.01) 2	2.1 [-1.9, 6.1]
	SF36 role physical score, Change value from baseline 95% CI	−0.87 (−2.85 to 1.10) −	−2.03 (−3.98 to −0.08)	1.16 [-1.62, 3.93]
	SF36 social functioning, Change value from baseline 95% CI	−0.72 (−3.01 to 1.57)	−2.71 (−4.97 to −0.46)	1.99 [-1.22, 5.21]
	Vitality score difference, Change value from baseline 95% CI	0.02 (−1.70 to 1.75)	−2.01 (−3.70 to −0.31)	2.03 [-0.39, 4.44]
	EuroQol, Change value from baseline 95% CI	−0.01 (−0.06 to 0.03)	−0.03 (−0.08 to 0.01)	0.02 [-0.04, 0.08]
	EuroQol Thermometer, Change value from baseline 95% CI	0.48 (−3.10 to 4.06)	−1.81 (−5.34 to 1.73)	2.28 [-2.75, 7.32]
Collard et al 2007[7]	6MWD Mean difference (90% CI)	Sildenafil, n = 14 49 (17.5 to 84.0)		
Chinese Medicine (Feiwi)				
Yu et al, 2016[8]		Feiwei granules, n=62	Control (Jinshuibao capsules), n=15	P-value
	MRC dyspnoea, mean (SD) 6 months Change value from baseline	-0.8 (0.8)	0.1 (1.0)	p=0.001
	SGRQ total score, mean (SD) 6 months Change value from baseline	-14 (19)	-3 (10)	p<0.05
	6MWT, m, mean (SD) 6 months Change value from baseline	48 (107)	30 (54)	p=ns
Zeng et al, 2015[9]				P-value
	Anxiety			P<0.05
	Depression			P<0.05
Riociguat				
Hoeper et al, 2013[10]		Riociguat, n=18(efficacy set)		95% CI
	6MWD, 12 weeks[c] Change value from baseline	25 (64)		(-8, 58)
Oxygen				
Visca et al, 2017[11]	Endpoint values (2 weeks) for:	Oxygen n = 41	No oxygen n = 43	
	Total KBILD	55[a]	52[a]	3.7 (1.8, 5.7) p<0.0001
	KBILD breathlessness + activity	42[a]	34[a]	8.7 (4.8, 12.6) p<0.0001
	KBILD chest symptoms	66[a]	59[a]	7.6 (1.9, 13.2) p=0.009
	KBILD psychological symptoms	56[a]	54[a]	2.4 (0.7, 5.5) p=0.12
	UCSD shortness of breath questionnaire	45[a]	48[a]	p<0.0001
	Total SGRQ score, mean (95% CI)	48.7 (42.9-54.6)	52.3 (46.6-58.1)	p=0.018
Schaeffer et al, 2017[12] (IPF subgroup only)	Dyspnoea Borg units[a] Rest Iso-time	Hyperoxia 0.3±0.9 2.7±2.3	Room air 0.2±0.6 4.2±3.3	 P = 0.34 P = 0.08

	Peak	5.9±3.7	5.8±3.2	P = 0.83
Corticosteroids				
Papiris et al 2015[13]		Ever treated, n=12	Never treated, n=12	P-value
	6MWD	272 (150-441)	271.5 (153-492)	0.932
Fiorucci et al 2008[14]		corticosteroids		
	Dyspnoea Prednisone Baseline value Endpoint value Prednisone plus cyclophosphamide Baseline value Endpoint value Prednisone plus colchicine Baseline value Endpoint value P value	 5.7 ± 1.3 8.8 ± 1.2 5.3 ± 1.3 8.9 ± 2 8.4 ± 2.5 6.3 ± 2.2 0.001		
Hope-Gill et al 2003[15]		Corticosteroids, n=6		
	Cough VAS Baseline value Endpoint value P value	 7.2 (0.8) 2.2 (2.5) P < 0.05		
	Total number of coughs P value for change	 P < 0.03		
Proton pump inhibitors				
Dutta et al 2019[16]		Omeprazole, n=23	Placebo, n=22	
	Geometric mean 24-h cough frequency (coughs/hour) Baseline value Endpoint value	 8.2 (95% CI 5.4 -12.7) 4.6 (95% CI 2.4 – 8.7)	 9.1 (95% CI 6.8 – 12.2) 8.3 (95% CI 5.3 – 12.9)	Ratio of geometric means adjusted for baseline 0.61 95% CI 0.34, 1.09
	Awake/daytime Baseline value Endpoint value	 10.8 (95% CI 6.8 – 17) 6.1 (95% CI 3.2 – 11.8)	 11.8 (95% CI 8.9 – 15.8) 10.7 (95% CI 6.7 – 17.2)	Ratio of geometric means adjusted for baseline 0.63 95% CI 0.35, 1.12
	Asleep/night-time Baseline value Endpoint value	 1.7 (95% CI 0.9 – 3.3) 1.1 (95% CI 0.6 to 2.0)	 2.3 (95% CI 1.1 – 4.7) 2.1 (95% CI 1.2 – 3.7)	Ratio of geometric means adjusted for baseline 0.55 95% CI 0.27, 1.15
	Symptoms of cough LCQ-total Baseline value Endpoint value LCQ-physical domain Baseline value Endpoint value LCQ-psychological domain Baseline value Endpoint value LCQ-social domain Baseline value	 15.3 (3.3) 15.3 (3.8) 5.1 (1.1) 5.0 (1.1) 5.0 (1.4) 5.0 (1.7) 5.2 (1.1)	 15.1 (3.2) 15.3 (3.6) 5.2 (1.0) 5.1 (1.1) 4.8 (1.2) 5.1 (1.3) 5.1 (1.3)	Adjusted between group difference -0.10 (95% CI-2.19, 1.98) 0.02 (95% CI -0.54, 0.57) -0.21 (95% CI -1.10, 0.68)

	Endpoint value	5.3 (1.3)	5.1 (1.4)	0.13 (95% CI -0.67, 0.94)
	Symptoms of reflux DeMRQ Baseline value Endpoint value GIQLI Baseline value Endpoint value RSI Baseline value Endpoint value	 0.85 (0.81) 0.65 (1.18) 106.7 (18.8) 105.6 (20.6) 14 (10.2) 14.2 (8.3)	 1.35 (1.14) 1.2 (1.24) 104 (18.2) 101.2 (21.2) 17 (9.4) 15.1 (11)	 Not done as model assumption not met Adjusted between group difference 2.15 (95% CI -7.2, 11.49) 0.67 (95% CI -4.77, 6.11)
	6MWD (m) Baseline value Endpoint value	 408.5 (102.6) 386.3 (130.6)	 372.4 (112.7) 381.1 (109.9)	Adjusted between group difference -30.4 (95% CI -68.9, 8.1)
Kilduff et al 2014[17]		Proton pump inhibitor, n=14		
	24-hour cough count, median (IQR) Baseline value Endpoint value P-value	 188 (338) 240 (382) p=0.7		
Thalidomide				
Horton et al, 2012[18]		Thalidomide , n=12	Placebo, n=12	Mean difference (95% CI) and p-value
	CQLQ			-11.4 (-15.7 to -7.0), p<0.001
	Cough VAS			-31.2 (-45.2 to -17.2), p<0.001
	SGRQ total			-11.7 (-18.6 to -4.8), p=0.001
	SGRQ symptom domain			-12.1 (-22.2 to -2.0), p=0.018
	SGRQ impact domain			-13.1 (-19.7 to -6.6), p<0.001
	SGRQ activity domain			-3.3 (-9.8 to 3.2), p=0.31
Horton et al 2008[19]		Thalidomide, n=11		
	SGRQ Baseline value Endpoint value P-value	 4.9 (0.3) 2.2 (1.6) P=0.03		
PA101 (cromolyn sodium)				
Birring et al 2016[20, 21]		PA101, n=23	Placebo, n=21	P-value
	Daytime cough frequency LCM (coughs/hr), combined periods, 14 days Baseline value Endpoint value	 55 39	 51 52	0.02
	24-h cough frequency, LCM (coughs/hour), 14 days Change value from baseline	29.1% (adjusted for placebo)		0.026
	24-h cough frequency, combined periods, least square means (95% CI) Change value from baseline, Day 14	0.71 (0.56, 0.90)	1.04 (0.81, 1.34)	Ratio of LS means 0.68 95% CI 0.49, 0.95, p=0.0245
	Nocturnal cough Change value from baseline, Day 14	NR	NR	Ratio of LS means 0.64 95% CI 0.26, 1.57, p=0.30
	Cough QoL, LCQ total score, 14 days Change value from baseline	1.1	0.01	LS mean difference 1.1 (95% CI -0.18, 2.33), p=0.09

	KBILD total score (QOL), 14 days Change value from baseline	0.5 (1.3)	-1.7 (1.3)	LS mean difference 2.2 (95% CI -0.76, 5.19), p=0.11
	6MWD (m) Baseline value Endpoint value	 408.5 (102.6) 386.3 (130.6)	 372.4 (112.7) 381.1 (109.9)	Adjusted between group difference -30.4 (95% CI -68.9, 8.1)
VRP700				
Satia et al 2014[22]	Number of coughs in the 4 h following treatment, mean (95% CI)	VRP700, n=20 136.8 (95% CI 80.3- 233.1)	Placebo, n=20 64.9 (95% CI 38.1–110.6)	P-value p<0.001
Opioids				
Allen et al 2005[23]		Morphine, n=11		
	Dyspnoea Baseline value Value at 15 min Value at 30 min P value	 83 (13) 36 (11) 36 (12) <0.0001		
Pulmonary Rehabilitation[#]				
		Pulmonary rehabilitation	Control	Effect size, mean difference (95% CI)
	6MWD			
Holland et al 2008[24] **(**IPF subgroup)	6MWD	25.05 (54.1)	8.93 (33.3)	16.12 [-13.32, 45.56]
Nishiyama et al 2008[25]	6MWD mean (SD)	42 (50.8)	-4 (57.7)	46.00 (5.81, 86.19)
Jackson et al 2014[26, 27]	6MWD mean (SD)	-6.2 (86.91)	-15.3 (42.89)	9.10 (-48.73, 66.93)
Vainshelboim et al, 2014[28-34]	6MWD mean (SD)	70.4 (77)	-10.6 (35.4)	81.00 (38.56, 123.44)
Dowman et al, 2017 [35-38] (IPF subgroup)	6MWD mean (SD)	29 (57)	0 (27)	29.00 (6.94, 51.09)
	6MWD Pooled effect	Random effect meta-analysis MD 35.24 m, 95% CI 13.77, 56.72, I2=46%		
	6MWD at longest follow up			
		Pulmonary rehabilitation	Control	Mean difference (95%CI)
Holland et al 2008[24] (IPF subgroup)	6MWD at longest follow up, mean (SD)	-19.15 (101.25)	3.93 (32.41)	-23.08 (-70.59, 24.43)
Vainshelboim et al, 2014[28-34]	6MWD at longest follow up, mean (SD)	-1 (86)	-49 (86)	48.00 (-15.71, 111.71)
Jarosch et al, 2016[39-41]	6MWD at longest follow up, mean (SD)	8 (72)	-6 (72)	14.00 (-44.43, 72.43)
Dowman et al, 2017 [35] (IPF subgroup)	6MWD at longest follow up, mean (SD)	-5 (57)	-10 (27)	5.00 (-17.06, 27.06)
	6MWD at longest follow up Pooled effect	Random effect meta-analysis MD 5.26 m, 95% CI -12.88, 23.40, I2 6%		
Jastrzebski et al, 2008[42]	6MWD Baseline value mean (SD) Endpoint value mean (SD)	Pulmonary rehabilitation (PR) 487.4 (100.2) 600.8 (93.7)	Control 485.6 (111.7) 544.5 (121.5)	
	Dyspnoea	PR 5.3 (2.2)	Control 5.2 (2.3)	

	Baseline value mean (SD) Endpoint value mean (SD)	3.8 (2.3)	4.2 (2.1)	
Arizono et al, 2014[43]	ISWT Change value	**10 weeks** 9.1 (15.7)%	 -5.1 (21.6)%	 P value (change) 0.01
	6MWD Baseline value mean (SD) Endpoint value mean (SD)	PR 477.7 (91) 504.4 (96.8)	Control 499.4 (66.6) 478.8 (78.7)	
Dowman et al, 2017 [35] (IPF subgroup)	Dyspnoea, mMRC, 9 weeks Baseline value Endpoint value Change value	PR 2 (1)	Control 2 (1)	Difference in change (95% CI) 0.009 (-0.4, 0.5)
	Dyspnoea, mMRC, 6 months Baseline value Endpoint value Change value	PR 2 (1) NR NR	Control 2 (1) NR NR	Difference in change (95% CI) -0.3 (-0.8, 0.1)
	Dyspnoea, CRDQ, 9 weeks Change value (95% CI)	PR 4	Control 0.5	Difference in change (95% CI) 3.1 (0.1, 6.0)
	Dyspnoea, CRDQ, 6 months Baseline value Endpoint value Change value	PR NR NR 2.8	Control NR NR 1	Difference in change (95% CI) 1.5 (-1.5, 4.6)
	Dyspnoea, UCSD SBQ, 9 weeks Baseline value Endpoint value Change value	PR 39 (23) NR NR	Control 47 (20) NR NR	Difference in change (95% CI) 6.5 (-2.5, 15.6)
	Dyspnoea, UCSD SBQ, 6 months Baseline value Endpoint value Change value	PR 39 (23) NR NR	Control 47 (20) NR NR	Difference in change (95% CI) -0.2 (-9.7, 9.2)
	Qol, SGRQ-I, 9 weeks Baseline value Endpoint value Change value	PR 49 (18) NR NR	Control 55 (19) NR NR	Difference in change (95% CI) -5.7 (-11.1, 0.3)
	Qol, SGRQ-I, 6 months Baseline value Endpoint value Change value	PR 49 (18) NR NR	Control 55 (19) NR NR	Difference in change (95% CI) -0.8 (-6.5, 5.0)
	Dyspnoea, CRDQ, 9 weeks Baseline value Endpoint value Change value	PR NR 2.5	Control NR[q] 0.2	Difference in change (95% CI) 2.0 (-0.3, 4.3)
	Dyspnoea, CRDQ, 6 months Baseline value Endpoint value Change value	PR NR[q] 1	Control NR[q] -0.5	Difference in change (95% CI) 1.1 (-1.3, 3.5)
Del Castillo et al 2017[44]	6MWD Change value at 12 weeks, mean	PR 40		

	P-value for change	0.1		
	MRC dyspnoea Change value at 12 weeks, mean P-value for change	PR 1.3 0.01		
Chehere et al 2019[45, 46]	6MWD Baseline value mean (SD) Endpoint values at 8 weeks mean (SD) P value	PR 425 (57) 448 (68) 0.01		
	SF-36 scores Physical summary score Baseline value mean (SD) Endpoint values at 8 weeks mean (SD) P value Physical functioning score Baseline value mean (SD) Endpoint values at 8 weeks mean (SD) P value Mental summary score Baseline value mean (SD) Endpoint values at 8 weeks mean (SD) P value	PR 54 (19) 60 (18) 0.10 55 (23) 63 (24) 0.004 60 (21) 66 (21) 0.14		
	Dyspnoea Baseline value mean (SD) Endpoint values at 8 weeks mean (SD) P value	 6.8 (2.1) 0.9 (1.3) 0.01		
	HADS Anxiety Baseline value mean (SD) Endpoint values at 8 weeks mean (SD) P value HADS depression Baseline value mean (SD) Endpoint values at 8 weeks mean (SD) P value	 7.6 (4.8) 6.7 (4.1) 0.53 5.2 (3.5) 5.3 (3.0) 0.87		
Nolan et al, 2018[47]	Dyspnoea: MRC Change from baseline (mean (95%CI))	PR -0.06 (-0.08 to -0.4)		
	Quality of life: KBILD Change from baseline (mean (95%CI))	PR 3.9 (2.0 to 5.7)		
Nolan et al, 2017[48]	Dyspnoea: MRC Change from baseline (mean (95%CI)	PR -0.6 (-0.8 to -0.4)		<0.001
	Dyspnoea: CRQ Change from baseline (mean (95%CI)	PR 5.0 (4.0 to 6.0)		<0.0001
	Quality of life: CRQ total Change from baseline (mean (95%CI)	PR 12.4 (9.4 to 15.4)		<0.0001

Ryerson et al, 2014[49-52]	6MWD Baseline value Endpoint value Change value	 358.25 (109.7) 410.5 (SD 94.9) 52.25 (SD 60.0)		0.00001
	Dyspnoea, UCSD SOBQ Baseline value Endpoint value Change value	UCSD SOBQ, n=29 45.9 (26.6) 35.9 (20.6) -10.1 (17.8)		0.005
	QoL, SGRQ total Baseline value Endpoint value Change value	SGRQ total, n=30 45.1 (17.8) 40.1 (17.8) -5.0 (8.6)		0.004
Jackson et al 2014[26, 27]	Dyspnoea, Borg, 3 months Baseline value Endpoint value Change value	PR 0.5 (SEM 0.3) 0.6 (SEM 0.3) NR	Control 0.2 (SEM 0.2) 0.6 (SEM 0.2) NR	NR
	Qol, SGRQ-I symptom score, 3 months Change value	PR -9.1 (22.2) 95% CI 24.0, 5.9	Control 15.5 (12.3) 95% CI 6.6, 24.3	p=0.01
	Qol, SGRQ-I symptom score, 6 months vs 3 months Change value	PR 7.2 (16.3) 95% CI -3.8, 18.1	Control -13.4 (28.0) 95% CI -33.5, 6.5	p=0.06
Vainshelboim et al, 2014[28-34]	Dyspnoea, MRC, 12 weeks Change value	PR -0.73 (0.8)	Control 0.35 (0.7)	P-value (for change) <0.001
	Dyspnoea, MRC, 11 months Change value	PR -0.4 (0.9)	Control 0.1 (0.7)	P-value (change) ns
	Qol, SGRQ, 12 weeks Change value	PR -6.9 (6.5)	Control 2.8 (3.6)	p<0.001
	Qol, SGRQ, 11 months Change value	PR -2 (7)	Control 4 (8)	p=ns
Rastogi et al, 2015[53]	6MWD Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 340 (47.21) 387 (63.57) P < 0.0001		
	Borg rest Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 0.14 (0.28) 0.07 (0.23) 0.429		
	Borg post-6MWD Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	 2.57 (1.09) 1.82 (0.98) 0.006		
Jarosch et al, 2016[39-41]	HADS anxiety, mean change value from baseline to 6 weeks HADS depression, mean change value from baseline to 6 weeks	PR -1.5 (2.7) -1.7 (2.3)	Control NR NR	

	Dyspnoea, CRDQ, 3 weeks Baseline value Endpoint value Change	PR NR	Control NR	
	Dyspnoea, CRDQ, 3 months Baseline value Endpoint value Change	PR 4.7 (1.7) 4.7	Control 4.5 (1.5) 3.9	NR
	Qol, SF-36 mental, 3 weeks Change value	PR 6.1 (7.9)	Control -1.0 (9.9)	P value NR
	Fatigue, CRDQ, 3 weeks Baseline value Endpoint value Change	CRDQ, 3 weeks NR		
	Fatigue, CRDQ, 3 months Baseline value Endpoint value Change	CRDQ, 3 months 4.4 4.3	 4.5 4.1	P value NR
Keyser et al 2015[54, 55][a]	6MWD (IPF subgroup) Baseline value, mean (SD) Endpoint value, mean (SD) P value	PR 426.67 (95.01) 472.44 (70.19) 0.006		
Kozu et al, 2011a[56]*	6MWD Grade 2 (mean difference (95% CI) at 8 wks) Grade 2 (p-value for mean difference) Grade 3 (mean difference (95% CI) at 8 wks) Grade 3 (p-value for mean difference) Grade 4 (mean difference (95% CI) at 8 wks) Grade 5 (mean difference (95% CI) at 8 wks) BDI and TDI Grade 2: mean difference at 8 wks (95% CI) Grade 3: mean difference at 8 wks (95% CI) Grade 4: mean difference at 8 wks (95% CI) Grade 5: mean difference at 8 wks (95% CI)	PR 31 (19, 44) P < 0.01 19 (4, 33) P < 0.05 9 (-1, 20) 0 (-8, 8) 1.6 (1.0, 2.3) 0.8 (0.1, 1.6) -0.2 (-0.8, 0.3) -0.6 (-1.2, -0.1)		
Rifaat et al, 2014[57, 58]	Dyspnoea: Modified Borg Scale Baseline value, mean (SD) Endpoint value, mean (SD) P value 6MWD Baseline value, mean (SD)	 5 (1.2) 3.7 (1.1) 0.001 281.8 (64.7)		

	Endpoint value, mean (SD) P value SGRQ score Baseline value, mean (SD) Endpoint value, mean (SD) P value	342.4 (60.01) 0.001 53.5 (19.5) 18.7 (15.2) 0.001		
Holland et al 2012[59, 60]	CRQ dyspnoea Change value at 8 weeks P-value (change at 8 weeks) P-value (change at 6 months) 6MWD Baseline value Endpoint at 8 weeks P-value (change at 8 weeks) 6MWD at longest follow up, mean (SD) P-value at longest follow up	PR (IPF subgroup) 2.7 (5.6) P < 0.05 NS 370 (127) NR P < 0.05 21 (58) NS		
Strookappe et al 2015[61]	6MWD Change value at 12 weeks, mean (SD) P value for change at 12 weeks 6MWD, % predicted Change value at 12 weeks, mean (SD) P value for change at 12 weeks Dyspnoea Borg scale: baseline, mean (SD) Borg scale: endpoint, mean (SD) Borg RPE scale: baseline, mean (SD) Borg RPE scale: endpoint, mean (SD) Fatigue FAS score: baseline, mean (SD) Fatigue FAS score: endpoint, mean (SD) FAS score: Improved n (%) FAS score: Stable n (%) FAS score: Deteriorated n (%)	PR 29.4 (73.6) 0.588 9.45 (19.4) 0.706 4.6 (2.0) 5.3 (2.1) 12.5 (3.0) 13.9 (2.6) 25.1 (5.6) 25.9 (9.9) 4 (33.3) NR for IPF NR for IPF		
Rammaert et al 2009[62, 63]	6MWD Baseline value mean SD Endpoint value mean (SD) P value VAS for QoL Baseline value mean (SD) Endpoint value P value Physical limitation on SF-36	PR 322 (97) 456 (163) 0.026 38 (8) 42 (12) 0.004 25% (26)		

	Baseline value Endpoint value P value for change Borg scale (relative to the number of steps using the step device) Baseline value mean (SD) Endpoint value P value Borg dyspnoea scale (6-min step test under O_2) Baseline value mean SD Endpoint value mean (SD) P value BDI score Baseline value mean SD Endpoint value mean (SD) P value MRC score Baseline value median IQR Endpoint value median IQR P value	49% (38) 0.047 0.017 (0.015) 0.008 (0.005) 0.026 4.5 (1.9) 3.8 (2.2) 0.78 5.8 (1.9) 6.0 (1.7) 0.23 1.5 (1 – 3) 2 (1 – 3) 0.18		
Ozalevli et al 2010[64]	6MWD Baseline value Endpoint value P value MRC scale Baseline value mean (SD) Endpoint value mean (SD) P value	PR 390.3 430.5 0.04 2.3 (1.2) 1.4 (1.3) 0.003		
Holland et al 2008[24]	SF36 functioning			Effect size mean difference (95% CI) 1.83 [-1.19, 4.85]
Kozu et al, 2011b[65]*				Change from baseline mean difference (95% CI) 1.9 [-1.1, 5]
Kozu et al, 2011a[56]*				Grade 2: mean difference (95% CI) = 6.6 (1.5, 11.6) Grade 3: mean difference (95% CI) = 11.2 (6.2, 16.2) Grade 4: mean difference (95% CI) = 0.3 (-1.8, 2.4) Grade 5: mean difference (95% CI) = -1.0 (-3.6, 1.6)
Jastrzebski et al, 2008[42]	SF36 functioning Baseline value mean (SD) Endpoint value at 12 weeks mean (SD)	PR 54.4 (23.6) 68.1 (22.3)	Control 54.3 (17.4) 62.5 (14.5)	

	P value	0.015	0.038	
Ozalevli et al 2010[64]	SF36 functioning Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 56 (5.7) 58.7 (7.3) 0.24		
Holland et al 2008[24]	SF36 role physical			Effect size mean difference (95% CI) 1.01 [0.27, 1.75]
Kozu et al, 2011b[65]*				Change from baseline mean difference (95% CI) 1.0 [-1.6, 3.6]
Kozu et al, 2011a[56]*				Grade 2: mean difference (95% CI) = 12.5 (4.6, 20.4) Grade 3: mean difference (95% CI) = 9.2 (0.8, 17.6) Grade 4: mean difference (95% CI) = 0.2 (-4.6, 4.8) Grade 5: mean difference (95% CI) = -0.8 (-2.6, 1.0)
Jastrzebski et al, 2008[42]	SF36 role physical Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 42.8 (32) 65.6 (31.5) 0.013	Control 44.6 (24.4) 64.3 (30.6) 0.059	
Ozalevli et al 2010[64]	SF36 role physical Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 25 (1.7) 68.3 (1.6) 0.01		
Holland et al 2008[24]	SF36 pain index			Effect size mean difference (95% CI) 0.69 [-0.95, 2.33]
Kozu et al, 2011b[65]*				Change from baseline mean difference (95% CI) -2.7 [-8.2, 2.7]
Kozu et al, 2011a[56]*				Grade 2: mean difference (95% CI) = 2.3 (-4.3, 6.5) Grade 3: mean difference (95% CI) = 4.9 (-6.9, 16.7) Grade 4: mean difference (95% CI) = -3.7 (-10.6, 3.2) Grade 5: mean difference (95% CI) = -0.9 (-13.9, 12.2)
Jastrzebski et al, 2008[42]	SF36 role pain index Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 68.9 (27.2) 75.7 (20.7) 0.182	Control 66.8 (22.2) 69.6 (17.8) 0.610	
Ozalevli et al 2010[64]	SF 36 pain index Baseline value mean (SD)	PR 67.3 (2.6)		

	Endpoint value at 12 weeks mean (SD) P value	72 (2.2) 0.4		
Holland et al, 2008[24]	SF36 general health perception			Effect size mean difference (95% CI) 2.67 [0.23, 5.09]
Kozu et al, 2011b[65]*				Change from baseline mean difference (95% CI) -0.2 [-2.8, 2.4]
Kozu et al, 2011a[56]*				Grade 2: mean difference (95% CI) = 10.3 (3.4, 17.1) Grade 3: mean difference (95% CI) = 7.9 (1.4, 14.4) Grade 4: mean difference (95% CI) = -1.8 (-4.5, 1.0) Grade 5: mean difference (95% CI) = -0.7 (-3.0, 1.6)
Jastrzebski et al, 2008[42]	SF36 general health perception Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 37.8 (17.7) 44.2 (22.4) 0.244	Control 37.4 (11.1) 42.4 (13.6) 0.028	
Ozalevli et al 2010[64]	SF 36 general health perception Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 57 (4.6) 74 (4.7) 0.04		
Holland et al, 2008[24]	SF36 vitality			Effect size mean difference (95% CI) 4.50 [2.24, 6.76]
Kozu et al, 2011b[65]*				Change from baseline mean difference (95% CI) 0.9 [-1.9, 3.6]
Kozu et al, 2011a[56]*				Grade 2: mean difference (95% CI) = 8.2 (2.4, 14.0) Grade 3: mean difference (95% CI) = 9.6 (2.7, 16.4) Grade 4: mean difference (95% CI) = 0.4 (-3.1, 3.9) Grade 5: mean difference (95% CI) = -2.9 (-10.0, 4.2)
Jastrzebski et al, 2008[42]	SF36 vitality Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 54.4 (18.2) 60 (16.4) 0.209	Control 52.5 (13.3) 57.1 (16.9) 0.196	
Ozalevli et al 2010[64]	SF36 vitality Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 52 (4.9) 55 (4.2) 0.4		
Holland et al, 2008[24]	SF36 social functioning			Effect size mean difference (95% CI) 1.73 [-0.05, 3.51]

Kozu et al, 2011b[65]*				Change from baseline mean difference (95% CI) -0.7 [-3.2, 1.8]
Kozu et al, 2011a[56]*				Grade 2: mean difference (95% CI) = 8.6 (1.0, 16.2) Grade 3: mean difference (95% CI) = 4.4 (-4.0, 12.9) Grade 4: mean difference (95% CI) = -0.7 (-4.3, 2.8) Grade 5: mean difference (95% CI) = -0.8 (-4.9, 3.3)
Jastrzebski et al, 2008[42]	SF36 social functioning Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 58.9 (23.5) 75.8 (30.8) 0.005	Control 58 (14.4) 68.7 (18.2) 0.05	
Ozalevli et al 2010[64]	SF36 social functioning Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 75.8 (2.7) 89.1 (1.8) 0.17		
Holland et al, 2008[24]	SF36 role emotional			Effect size mean difference (95% CI) 0.10 [-0.90, 1.10]
Kozu et al, 2011b[65]*				Change from baseline mean difference (95% CI) -0.9 [-5.4, 3.6]
Kozu et al, 2011a[56]*				Grade 2: mean difference (95% CI) = 7.3 (2.2, 12.4) Grade 3: mean difference (95% CI) = 7.4 (2.3, 12.3) Grade 4: mean difference (95% CI) = -1.0 (-6.0, 4.0) Grade 5: mean difference (95% CI) = -1.4 (-3.5, 0.7)
Jastrzebski et al, 2008[42]	SF36 role emotional Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 68.8 (39.4) 70.8 (29.5) 1.00	Control 69 (44.3) 78.6 (28.1) 0.352	
Ozalevli et al 2010[64]	SF36 role emotional Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 29 (1.3) 65 (1.4) 0.02		
Holland et al, 2008[24]	SF36 mental health index			Effect size mean difference (95% CI) 4.52 [1.10, 7.94]
Kozu et al, 2011b[65]*				Change from baseline mean difference (95% CI) 1.9 [-1.1, 5]

Kozu et al, 2011a[56]*				Grade 2: mean difference (95% CI) = 6.9 (2.3, 11.4) Grade 3: mean difference (95% CI) = 8.5 (-1.4, 18.4) Grade 4: mean difference (95% CI) = 2.4 (-2.9, 7.6) Grade 5: mean difference (95% CI) = -2.7 (-8.2, 2.9)
Jastrzebski et al, 2008[42]	SF36 mental health index Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 64.2 (17.7) 68.7 (16.8) 0.187	Control 65.1 (17.9) 66.3 (20.2) 0.415	
Ozalevli et al 2010[64]	SF36 role mental health index Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 49.9 (6.7) 56.8 (5.4) 0.14		
Jastrzebski et al, 2008[42]	SF36 physical cumulative score Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 38.4 (8.2) 44.8 (6.0) 0.03	Control 36.1 (9.1) 42.3 (5.8) 0.016	
	SF36 mental cumulative score Baseline value mean (SD) Endpoint value at 12 weeks mean (SD) P value	PR 46.6 (9.9) 47.8 (11.22) 0.756	Control 46.5 (10.9) 47.8 (11.6) 0.615	
Holland et al, 2008[24]	MRC Scale			Effect size mean difference (95% CI) -0.84[-1.73, 0.05]
	CRDQ dyspnoea			Effect size mean difference (95% CI) 5.43 [1.34, 9.52]
	CRDQ fatigue			4.67 [1.76, 7.58]
	CRDQ mastery			3.33 [0.82, 5.84]
	CRDQ emotional			7.44 [0.87, 14.01]
Kozu et al, 2011b[65]*	MRC Scale			Change from baseline mean difference (95% CI) -0.4 (-0.6, -0.3)
Nishiyama et al 2008[25]	Baseline Dyspnoea Index			Effect size mean difference (95% CI) 0.4 [-0.6, 1.4]
	SGRQ total score			-6.1 [-11.7, -0.5]
	SGRQ symptom score			-5.7 [-18.7, 7.2]
	SGRQ activity score			-5.8 [-14.7, 3.1]
	SGRQ impact score			-6.2 [-12.8, 0.3]

Swigris et al 2011[66, 67]	6MWD			Change from baseline mean difference (95% CI) 61.6 [-19.08, 142.22]
	Fatigue Severity Scale			-1.5 [-2.48, -0.52]
	General Anxiety Disorder 7			-1.4 [-3.36, 0.56]
	Patients Health Questionnaire 8			-0.9 [-2.27, 0.47]
	Pittsburgh Sleep Total			0.9 [-0.67, 2.47]
	SF36 Physical Functioning			1.2 [-3.11, 5.51]
	Role physical			1.5 [-2.42, 5.42]
	Bodily Pain			2.7 [-2.59, 7.99]
	General Health			1.4 [-4.09, 6.89]
	Vitality			3.6 [-0.71, 7.91]
	Social Functioning			1.9 [-2.41, 6.21]
	Role emotional			-1.9 [-10.33, 6.53]
	Mental health			1.6 [-1.73, 4.93]
	Physical component summary			3.0 [-1.12, 7.12]
	Mental Component summary			0.3 [-5.19, 5.79}
Non-pharmacological interventions				
Case conference				
Bajwah et al, 2015[68, 69]		Fast track Group, n=26	Waiting list Group, n=27	Mean change difference (95% CI); Effect size (95% CI)
	POS, mean (SD) Change value from baseline at 4 weeks	-5.7 (7.5)	-0.4 (8.0)	-5.3 (-9.8 to 0.7); -0.7 (-1.2 to -0.1), p=0.02
	D 12, mean (SD) Change value from baseline at 4 weeks	-0.8 (7.2)	−0.6 (21.3)	Effect size −0.3 (−0.9 to 0.3)
	KBILD, mean (SD) Change value from baseline at 4 weeks	3.5 (11.0)	−2.6 (21.3)	Effect size 0.6 (0.0 to 1.2)
	SGRQ total score, mean (SD) Change value from baseline at 4 weeks	-2.8 (14.9)	0.7 (10.5)	Effect size −0.9 (−1.5 to −0.3)
	MRC breathlessness scale, median (IQR) Baseline value Endpoint value (4 weeks)	 4 (4-5) 4 (4-5), n=23	 5 (4-5) 5 (4-5), n=24	
	HADS anxiety , mean (SD) Change value from baseline at 4 weeks	−1.7 (3.3)	1.2 (4.8))	Effect size −0.6 (−1.1 to 0.0)
	HADS depression, mean (SD) Change value from baseline at 4 weeks	0.3 (3.2)	1.5 (4.12)	Effect size −0.7 (−1.3 to −0.1)
	HADS total, mean (SD) Change value from baseline at 4 weeks	−1.4 (5.0)	2.8 (8.1)	Effect size −0.7 (−1.2 to −0.1)
Disease Management Programme				
Lindell et al 2010[70]		Intervention, n=10	Usual care, n=11	P-value
	Beck Anxiety Index scores Endpoint value	 15.13 (6.92)	 8.56 (6.95)	 P=0.077
	Beck Depression Endpoint value	 9.71 (4.34)	 9.44 (4.35)	 P = NS
	SF 36 Physical component Endpoint value	 31.06 (4.61)	 36.04 (4.63)	 P=0.038

Patient and partner empowerment programme (PPEPP)				
van Manen et al, 2017[71, 72]		PPEPP, n=13	Control Group, n=7	
	K-BILD total score, median (range) Change value from baseline, 3 months	p=ns	p=0.03	
	MRC dyspnoea scale, median (range) Change value from baseline, 3 months	p=ns	NR	
	EQ5D-5L, median (range) Change value from baseline, 3 months	p=ns	p=0.03	
	HADS total	p=ns	P=0.04	

[a]Data obtained from authors. *Grade 3, 4 and 5 had severe disease defined as DLCO, % pred < 45.

MID = Minimal Important Difference [#]studies in which patients had severe disease (DLCO, % pred < 45) are italicised. 6MWD = 6 Minute Walking Distance, ADL = Activities of Daily Living, CRQ = Chronic Respiratory Disease questionnaire, CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review questionnaire, DeMRQ = De Meester reflux-related symptoms questionnaire, D-12 = Dyspnea-12, GIQLI = Gastrointestinal Quality of Life Index, HADS = Hospital Anxiety and Depression scale, KBILD = King's Brief Interstitial Lung Disease questionnaire, LCM = Leicester Cough Monitor, LCQ = Leicester Cough Questionnaire, LCADL = London Chest Activity of Daily Living scale, MRC = Medical Research Council, NRS = Numerical Rating Scale, POS = Palliative care Outcome Scale, POMS = Profile Of Mood State test, SF-36 = Short Form 36 health survey questionnaire, SGRQ = St Georges Respiratory Questionnaire, UCSDBQ = University of California San Diego Shortness of Breath Questionnaire, VAS = Visual Analogue Scale

References

1. Corte TJ, Keir GJ, Dimopoulos K, Howard L, Corris PA, Parfitt L, Foley C, Yanez-Lopez M, Babalis D, Marino P, Maher TM, Renzoni EA, Spencer L, Elliot CA, Birring SS, O'Reilly K, Gatzoulis MA, Wells AU, Wort SJ, Group BS. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *American Journal of Respiratory & Critical Care Medicine* 2014: 190(2): 208-217.
2. Keir G, Corte T, Parfitt L, Maher T, Marino P, Renzoni E, Dimopoulos K, Gatzoulis M, Madden B, Howard L, Corris P, O'Reilly K, Hope-Gill B, Birring S, Wells A, Wort SJ. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia: A randomized, double-blind, placebo-controlled study. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2013: 42(no pagination).
3. King TE, Jr., Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, Valeyre D, Leconte I, Morganti A, Roux S, Behr J. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *American Journal of Respiratory & Critical Care Medicine* 2011: 184(1): 92-99.
4. King TE, Jr., Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stahler G, Leconte I, Roux S, Raghu G. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008: 177(1): 75-81.
5. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010: 363(7): 620-628.
6. Jackson RM, Glassberg MK, Ramos CF, Bejarano PA, Butrous G, Gomez-Marin O. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. *Lung* 2010: 188(2): 115-123.
7. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest* 2007: 131(3): 897-899.
8. Yu Y, Sun Z, Shi L, Zhang Y, Zhou Z, Zhang S, Chao E. Effects of Feiwei granules in the treatment of idiopathic pulmonary fibrosis: a randomized and placebo-controlled trial. *Journal of Traditional Chinese Medicine* 2016: 36(4): 427-433.
9. Zeng ZY. Recent study on traditional Chinese medicine foot bath combined with traditional Chinese and western medicine nursing for IPF. *Chinese community doctors [zhong guo she qu yi shi]* 2015: 31(14): 143-146.
10. Hoeper MM, Halank M, Wilkens H, Gunther A, Weimann G, Gebert I, Leuchte HH, Behr J. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. *European Respiratory Journal* 2013: 41(4): 853-860.
11. Visca D, Mori L, Tsipouri V, Canu S, Bonini M, Pavitt M, Fleming S, Firouzi A, Farquhar M, Leung E, Hogben C, De Lauretis A, Kokosi M, Lee J, Lyne R, Rippon N, Chetta A, Russell AM, Saunders P, Kouranos V, Margaritopoulos G, Maher TM, Stockford A, Cullinan P, Hopkins N, Birring S, Wells AU, Whitty J, Banya W, Adamali H, Spencer L, Sestini P, Renzoni EA. Ambox: A Randomised Controlled, Crossover Trial Evaluating The Effects Of Ambulatory Oxygen On Health Status In Patients With Fibrotic Interstitial Lung Disease. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
12. Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, Mitchell RA, Sheel AW, Khalil N, Camp PG, et al. Effects of hyperoxia on dyspnoea and exercise endurance in fibrotic interstitial lung disease. *The european respiratory journal* 2017: 49(5).
13. Papiris SA, Kagouridis K, Kolilekas L, Papaioannou AI, Roussou A, Triantafillidou C, Baou K, Malagari K, Argentos S, Kotanidou A, Karakatsani A, Manali ED. Survival in Idiopathic pulmonary fibrosis acute exacerbations: the non-steroid approach. *BMC Pulmonary Medicine* 2015: 15: 162.

14. Fiorucci E, Lucantoni G, Paone G, Zotti M, Li BE, Serpilli M, Regimenti P, Cammarella I, Puglisi G, Schmid G. Colchicine, cyclophosphamide and prednisone in the treatment of mild-moderate idiopathic pulmonary fibrosis: comparison of three currently available therapeutic regimens. *Eur Rev Med Pharmacol Sci* 2008: 12(2): 105-111.
15. Hope-Gill BD, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003: 168(8): 995-1002.
16. Dutta P, Funston W, Mossop H, Ryan V, Jones R, Forbes R, Sen S, Pearson J, Griffin SM, Smith JA, Ward C, Forrest IA, Simpson AJ. Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. *Thorax* 2019.
17. Kilduff CE, Counter MJ, Thomas GA, Harrison NK, Hope-Gill BD. Effect of acid suppression therapy on gastroesophageal reflux and cough in idiopathic pulmonary fibrosis: an intervention study. *Cough (London, England)* 2014: 10: 4.
18. Horton MR, Santopietro V, Mathew L, et al. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: A randomized trial. *Annals of Internal Medicine* 2012: 157(6): 398-406.
19. Horton MR, Danoff SK, Lechtzin N. Thalidomide inhibits the intractable cough of idiopathic pulmonary fibrosis. *Thorax* 2008: 63: 749-749.
20. Birring S, Wijsenbeek M, Al SA, Tutuncu A, Morice A. Significant improvement in refractory chronic cough with inhaled PA101 in patients with idiopathic pulmonary fibrosis: Results from phase 2 trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
21. Birring SS, Wijsenbeek MS, Agrawal S, van den Berg JWK, Stone H, Maher TM, Tutuncu A, Morice AH. A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial. *The Lancet Respiratory Medicine* 2017: 08: 08.
22. Satia I, Badri H, Dockry R, Chaudhuri N, Brown G, Abbott-Banner K, Smith JA. A randomised, double-blind, placebocontrolled crossover study to assess the efficacy of a single dose of 100 mg of VRP700 by inhalation in reducing the frequency and severity of cough in adult patients with idiopathic pulmonary fibrosis. *Thorax* 2015: 70: A52.
23. Allen S, Raut S, Woollard J, Vassallo M. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. *Palliative Medicine* 2005: 19(2): 128-130.
24. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax, 2008; pp. 549-554.
25. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S, Nishimura K, Taniguchi H. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008: 13(3): 394-399.
26. Jackson RM, Gomez-Marin OW, Ramos CF, Sol CM, Cohen MI, Gaunaurd IA, Cahalin LP, Cardenas DD. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. *Lung* 2014: 192(3): 367-376.
27. Jackson R, Ramos C, Cardenas D, Sol C, Cohen M, Gaunaurd I. Effects of aerobic and strength training on symptoms and exercise capacity of IPF patients [Abstract]. European Respiratory Journal, 2012; p. 672s [P3686].
28. Vainshelboim B, Oliveira J, Yehoshua L, Weiss I, Fox BD, Fruchter O, Kramer MR. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. *Respiration* 2014: 88(5): 378-388.

29. Vainshelboim B, Oliveira J, Fox B, Kramer M. Effect of exercise pulmonary rehabilitation on long-term outcomes in idiopathic pulmonary fibrosis. European respiratory journal, 2014.
30. Vainshelboim B, Oliveira J, Fox BD, Yehoshua L, Fruchter O, Kramer MR. Effect of exercise pulmonary rehabilitation on long-term outcomes in idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2014: 189(no pagination).
31. Vainshelboim B, Oliveira J, Yohoshua L, Wais I, Kramer MR. Effect of Pulmonary Rehabilitation Program on Exercise Tolerance and Functional Capacity in Patients with Idiopathic Pulmonary Fibrosis. *Medicine and Science in Sports and Exercise* 2013: 45(5): 543-543.
32. 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): 345-354.
33. Vainshelboim B, Fox BD, Kramer MR, Izhakian S, Gershman E, Oliveira J. Short-Term Improvement in Physical Activity and Body Composition After Supervised Exercise Training Program in Idiopathic Pulmonary Fibrosis. *Archives of Physical Medicine & Rehabilitation* 2016: 97(5): 788-797.
34. Vainshelboim B, Kramer MR, Fox BD, Izhakian S, Sagie A, Oliveira J. Supervised exercise training improves exercise cardiovascular function in idiopathic pulmonary fibrosis. *European journal of physical & rehabilitation medicine* 2016: 19.
35. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, Glaspole I, Goh NS, Southcott AM, Burge AT, Gillies R, Martin A, Holland AE. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax* 2017: 17.
36. Dowman L, McDonald CF, Hill C, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge A, Ndongo R, Martin A, Holland AE. The benefits of exercise training in interstitial lung disease: protocol for a multicentre randomised controlled trial. *BMC Pulmonary Medicine* 2013: 13: 8.
37. Dowman L, McDonald C, Hill C, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge A, Ndongo R, Martin A, Holland A. Effect of disease aetiology on response to exercise training in patients with interstitial lung disease. *Respirology* 2015: 20: 58.
38. Dowman LM, McDonald CF, Hill CJ, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge AT, Ndongo R, Martin A, Holland AE. 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: 191(no pagination).
39. Jarosch I, Schneeberger T, Gloeckl R, Kreuter M, Neurohr C, Prasse A, Behr J, Kenn K. Effects of a 3-week pulmonary rehabilitation program in patients with idiopathic pulmonary fibrosis-a randomized, controlled trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
40. Jarosch I, Schneeberger T, Gloeckl R, Kreuter M, Benstz J, Frankenberger M, Neurohr C, Prasse A, Behr J, Kenn K. Different Effects Of Pulmonary Rehabilitation In Anxious Vs. Non-Anxious Patients With Idiopathic Pulmonary Fibrosis - A Pilot Study. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
41. Schneeberger T, Glockl R, Jarosch I, Behr J, Neurohr C, Frankenberger M, Prasse A, Kreuter M, Kenn K. Effects of a 3-week inpatient pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis - a randomized, controlled trial. *Wiener Klinische Wochenschrift* 2016: 128(19-20): 779-780.
42. Jastrzebski D, Kozielski J, Zebrowska A. [Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis with inspiratory muscle training]. *Pneumonologia i alergologia polska* 2008: 76(3): 131-141.

43. Arizono S, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, Ogawa T, Watanabe F, Nishiyama O, Nishimura K, Kozu R, Tabira K. Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis. *Respiratory Care* 2014: 59(7): 1108-1115.
44. Del Castillo NT, Paredes L, Shek N, Gutierrez HH, Betancourt-Pena J. Benefits of Pulmonary Rehabilitation in Patients With Idiopathic Pulmonary Fibrosis and Other Interstitial Lung Diseases. *Chest* 2017: 152(4): 982A-982A.
45. Chehere B, Bougault V, Chenivesse C, Grosbois J-M, Wallaert B. Cardiorespiratory adaptation in a 6-minute walk test by fibrotic idiopathic interstitial pneumonia patients who did or did not respond to pulmonary rehabilitation. *European journal of physical and rehabilitation medicine* 2018.
46. Chehere B, Bougault V, Chenivesse C, Grosbois JM, Wallaert B. Cardiorespiratory adaptation during 6-Minute Walk Test in fibrotic idiopathic interstitial pneumonia patients who did or did not respond to pulmonary rehabilitation. *Eur J Phys Rehabil Med* 2019: 55(1): 103-112.
47. Nolan CM, Maddocks M, Maher TM, Patel S, Barker RE, Jones SE, Kwan H, Mehta B, Hogg L, Tuffnell R, George PM, Cullinan P, Man WD. Improvement in Gait Speed with Pulmonary Rehabilitation Is Associated with Increased Survival in Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2018: 197.
48. Nolan CM, Maddocks M, Delogu V, Patel S, Barked RE, Mehta B, Hogg L, Tuffnell R, Canavan JL, Jonesi SE, Koni SS, Maher TM, Cullinan P, Man WD. Responsiveness And Minimum Clinically Important Difference (mcid) Of The 4 Metre Gait Speed (4mgs) In Fibrotic Interstitial Lung Disease. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
49. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, Khalil N, Collard HR, Garvey C. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respiratory Medicine* 2014: 108(1): 203-210.
50. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp P, Wilcox PG, Khalil N, Garvey CM, Collard HR. Pulmonary rehabilitation improves long-term quality of life in patients with interstitial lung disease. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2013: 187(no pagination).
51. Ryerson CJ, Cayou C, Topp FJ, Hilling L, Wilcox PG, Khalil N, Collard HR, Garvey CM. Pulmonary rehabilitation in interstitial lung disease: Predictors of success. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2012: 185(no pagination).
52. Ryerson CJ, Topp F, Cayou C, Hilling L, Camp P, Khalil N, Wilcox PG, Collard HR, Garvey CM. A low baseline 6mwd predicts greater improvement from pulmonary rehabilitation in interstitial lung disease. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2013: 187(no pagination).
53. Rastogi SA, Koltharkar M, Udwadia ZF. Prospective study of pulmonary rehabilitation in interstitial lung disease in resource limited setting: An Indian experience. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2015: 191(no pagination).
54. Keyser RE, Woolstenhulme JG, Chin LM, Nathan SD, Weir NA, Connors G, Drinkard B, Lamberti J, Chan L. Cardiorespiratory function before and after aerobic exercise training in patients with interstitial lung disease. *Journal of Cardiopulmonary Rehabilitation & Prevention* 2015: 35(1): 47-55.
55. Keyser RE, Christensen EJ, Chin LM, Woolstenhulme JG, Drinkard B, Quinn A, Connors G, Weir NA, Nathan SD, Chan LE. Changes in fatigability following intense aerobic exercise training in patients with interstitial lung disease. *Respiratory Medicine* 2015: 109(4): 517-525.

56. 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): 1196-1202.
57. Rifaat N, Anwar E, Ali YM, Ellabban A, Hasan AA. Value of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Egyptian Journal of Chest Diseases and Tuberculosis* 2014: 63(4): 1013-1017.
58. 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: 44(no pagination).
59. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. *Respiratory Medicine* 2012: 106(3): 429-435.
60. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Benefits of exercise training are related to disease severity in idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2011: 183(1 MeetingAbstracts).
61. Strookappe B, Elfferich M, Swigris J, Verschoof A, Veschakelen J, Knevel T, Drent M. Benefits of physical training in patients with idiopathic or end-stage sarcoidosis-related pulmonary fibrosis: a pilot study. *Sarcoidosis Vasculitis & Diffuse Lung Diseases* 2015: 32(1): 43-52.
62. Rammaert B, Leroy S, Cavestri B, Wallaert B, Grosbois JM. [Home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis]. *Rev Mal Respir* 2009: 26(3): 275-282.
63. Rammaert B, Leroy S, Cavestri B, Wallaert B, Grosbois JM. Home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis. *Revue des Maladies Respiratoires* 2011: 28(7): e52-57.
64. Ozalevli S, Karaali HK, Ilgin D, Ucan ES. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Multidisciplinary Respiratory Medicine* 2010: 5(1): 31-37.
65. Kozu R, Senjyu H, Jenkins SC, 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.
66. Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, Wamboldt FS. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. *Respir Care* 2011: 56(6): 783-789.
67. Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, Wamboldt FS. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis.[Erratum appears in Respir Care. 2013 Apr;58(4):e51]. *Respiratory Care* 2011: 56(6): 783-789.
68. Bajwah S, Ross JR, Wells AU, Mohammed K, Oyebode C, Birring SS, Patel AS, Koffman J, Higginson IJ, Riley J. Palliative care for patients with advanced fibrotic lung disease: a randomised controlled phase II and feasibility trial of a community case conference intervention. *Thorax* 2015: 70(9): 830-839.
69. Bajwah S, Higginson IJ, Wells AU, Koffman J, Ross JR, Birring SS. Developing and evaluating a hospital2home palliative care service for patients with advanced progressive idiopathic fibrotic interstitial lung disease: Phase 0-II [Abstract]. Palliative medicine, 2012; p. 545.
70. Lindell KO, Olshansky E, Song M, Zullo TG, Gibson KF, Kaminski N, Hoffman LA. Impact of a disease-management program on symptom burden and health-related quality of life in patients with idiopathic pulmonary fibrosis and their care partners. *Heart & Lung* 2010: 39(4): 304-314.

71. van Manen MGJ, van 't Spiker A, Tak NC, Baars CT, Jongenotter SM, van Roon LR, Kraan J, Hoogsteden HC, Wijsenbeek MS. Patient and partner empowerment programme for idiopathic pulmonary fibrosis. *European Respiratory Journal* 2017: 49: 1601596 [https://doi.org/1601510.1601183/13993003.13901596-13992016].
72. Van Manen M, Van't Spijker A, Tak N, Baars C, Jongenotter S, Van Roon L, Kraan J, Wijsenbeek M. Patient and partner "empowerment" program in idiopathic pulmonary fibrosis (ppepp): Improving quality of life in patients and their partners. *Qjm* 2016: 109: S46.

Suppl 7 Adverse event data

Interventions	Study	Adverse events	Type of intervention		Difference between periods (95% CI), p-value or both
Bosentan	**Corte et al, 2014[1, 2]**		**Bosentan**	**Placebo**	
		Serious adverse events, % Respiratory Hepatic Heart failure Other	 20, n = 40 5, n = 40 5, n = 40 12.5, n = 40	 40, n = 20 5, n = 20 5, n = 20 15, n = 20	
		Deaths, %	7.5	15	
	King et al, 2011[3]	% of patients with AEs	97.5, n=407	97.1, n=209	
		% of patients with serious AEs	31.8, n=407	35.4, n=209	
	King Jr et al, 2008[4]	% of patients with serious AEs	29.7, n=74	34.5, n=84	
Sildenafil			**Sildenafil**	**Placebo**	
	Collard et al, 2007[5]	% of patients with AEs	36, n=14		
	Jackson et al, 2010[6]	% of patients with AEs	43, n=14	6, n=15	
	Zisman et al, 2010[7]	% of patients with AEs	89.9, n=89	86.8, n=91	
		% of patients with serious AEs	14.6, n=89	16.5, n=91	
Chinese Medicine	**Yu et al, 2016[8]**		**Feiwi, n=62**	**Control, n=15**	
		Serious treatment-related	0	0	
		Changes in ECG	0	0	
Riociguat	**Hoeper et al, 2013[9]**		**Riociguat, n=22 (safety set)**		
		Serious adverse events, n	16 (25 events)		
		Total AEs during 12 week and 12 month study combined, n events - n treatment emergent (%) - % drug related	104 86 (83) 70		
Oxygen	**Visca et al, 2017[10]**	Serious AEs (including deaths) equally distributed across both groups			
Corticosteroids	**Papiris et al, 2015(7)**	Deaths	8 /11 (72.7%)	3/6 (50%)	0.685
	Fiorucci et al, 2008[11]	Hyperglycaemia was observed in 5 patients on prednisone (45%) and two on prednisone plus colchicine (20%). Mild gastrointestinal side effects (e.g. diarrhoea, nausea) were observed using prednisone plus cyclophosphamide (33%) or prednisone plus colchicine (30%). Myelodepression was observed in 3 patients treated with prednisone plus cyclophosphamide and therapy was discontinued.			
Thalidomide	**Horton et al, 2008[12]**	The most common thalidomide-associated adverse events were dizziness and constipation			
	Horton et al,		**Thalidomide, n =**	**Placebo, n = 23**	

	2012[13]		**22**	
		% of patients with AEs	77, n=17	22, n=5
		% with serious adverse event	0, n = 0	4, n = 1
Proton pump inhibitor	**Dutta et al, 2019[14]**		**Omeprazole, n = 23**	**Placebo, n =**
		Adverse events, %		
		Lower respiratory tract infection	26	14
		Vomiting	9	18
		Urinary tract infection	9	0
		Abdominal pain	13	14
		Cough	13	5
PA101 (cromolyn sodium)	**Birring et al, 2016[15]**		**PA101, n=23**	**Placebo, n=21**
		Serious AEs	0	0
Pulmonary rehabilitation	**Holland et al, 2008[16]**	No adverse events were recorded		
	Kozu et al, 2011[17]	No adverse events were recorded		
	Keyser et al, 2015[18]	No serious adverse events were recorded		
	Ozalevli et al, 2010[19]	All patients stated that they had not experienced any problems such as dyspnoea and fatigue when performing their exercises		
	Vainshelboim et al, 2014[20]	No serious adverse events were recorded		

References

1. Corte TJ, Keir GJ, Dimopoulos K, Howard L, Corris PA, Parfitt L, Foley C, Yanez-Lopez M, Babalis D, Marino P, Maher TM, Renzoni EA, Spencer L, Elliot CA, Birring SS, O'Reilly K, Gatzoulis MA, Wells AU, Wort SJ, Group BS. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *American Journal of Respiratory & Critical Care Medicine* 2014: 190(2): 208-217.
2. Keir G, Corte T, Parfitt L, Maher T, Marino P, Renzoni E, Dimopoulos K, Gatzoulis M, Madden B, Howard L, Corris P, O'Reilly K, Hope-Gill B, Birring S, Wells A, Wort SJ. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia: A randomized, double-blind, placebo-controlled study. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2013: 42(no pagination).
3. King TE, Jr., Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, Valeyre D, Leconte I, Morganti A, Roux S, Behr J. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *American Journal of Respiratory & Critical Care Medicine* 2011: 184(1): 92-99.
4. King TE, Jr., Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stahler G, Leconte I, Roux S, Raghu G. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008: 177(1): 75-81.
5. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest* 2007: 131(3): 897-899.
6. Jackson RM, Glassberg MK, Ramos CF, Bejarano PA, Butrous G, Gomez-Marin O. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. *Lung* 2010: 188(2): 115-123.
7. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010: 363(7): 620-628.
8. Yu Y, Sun Z, Shi L, Zhang Y, Zhou Z, Zhang S, Chao E. Effects of Feiwei granules in the treatment of idiopathic pulmonary fibrosis: a randomized and placebo-controlled trial. *Journal of Traditional Chinese Medicine* 2016: 36(4): 427-433.
9. Hoeper MM, Halank M, Wilkens H, Gunther A, Weimann G, Gebert I, Leuchte HH, Behr J. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. *European Respiratory Journal* 2013: 41(4): 853-860.
10. Visca D, Mori L, Tsipouri V, Canu S, Bonini M, Pavitt M, Fleming S, Firouzi A, Farquhar M, Leung E, Hogben C, De Lauretis A, Kokosi M, Lee J, Lyne R, Rippon N, Chetta A, Russell AM, Saunders P, Kouranos V, Margaritopoulos G, Maher TM, Stockford A, Cullinan P, Hopkins N, Birring S, Wells AU, Whitty J, Banya W, Adamali H, Spencer L, Sestini P, Renzoni EA. Ambox: A Randomised Controlled, Crossover Trial Evaluating The Effects Of Ambulatory Oxygen On Health Status In Patients With Fibrotic Interstitial Lung Disease. *American Journal of Respiratory and Critical Care Medicine* 2017: 195.
11. Fiorucci E, Lucantoni G, Paone G, Zotti M, Li BE, Serpilli M, Regimenti P, Cammarella I, Puglisi G, Schmid G. Colchicine, cyclophosphamide and prednisone in the treatment of mild-moderate idiopathic pulmonary fibrosis: comparison of three currently available therapeutic regimens. *Eur Rev Med Pharmacol Sci* 2008: 12(2): 105-111.
12. Horton MR, Danoff SK, Lechtzin N. Thalidomide inhibits the intractable cough of idiopathic pulmonary fibrosis. *Thorax* 2008: 63: 749-749.
13. Horton MR, Santopietro V, Mathew L, et al. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: A randomized trial. *Annals of Internal Medicine* 2012: 157(6): 398-406.
14. Dutta P, Funston W, Mossop H, Ryan V, Jones R, Forbes R, Sen S, Pearson J, Griffin SM, Smith JA, Ward C, Forrest IA, Simpson AJ. Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. *Thorax* 2019.

15. Birring S, Wijsenbeek M, Al SA, Tutuncu A, Morice A. Significant improvement in refractory chronic cough with inhaled PA101 in patients with idiopathic pulmonary fibrosis: Results from phase 2 trial. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2016: 48(no pagination).
16. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax, 2008; pp. 549-554.
17. 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): 1196-1202.
18. Keyser RE, Woolstenhulme JG, Chin LM, Nathan SD, Weir NA, Connors G, Drinkard B, Lamberti J, Chan L. Cardiorespiratory function before and after aerobic exercise training in patients with interstitial lung disease. *Journal of Cardiopulmonary Rehabilitation & Prevention* 2015: 35(1): 47-55.
19. Ozalevli S, Karaali HK, Ilgin D, Ucan ES. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Multidisciplinary Respiratory Medicine* 2010: 5(1): 31-37.
20. Vainshelboim B, Oliveira J, Yehoshua L, Weiss I, Fox BD, Fruchter O, Kramer MR. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. *Respiration* 2014: 88(5): 378-388.