National Clinical Guideline Centre

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Diagnosis and management of idiopathic pulmonary fibrosis

Appendices

Clinical Guideline

Appendices A-S

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Appendices

Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Idiopathic pulmonary fibrosis: the diagnosis and management of suspected idiopathic pulmonary fibrosis

1.1 Short title

Idiopathic pulmonary fibrosis

2 The remit

The Department of Health has asked NICE: 'To produce a clinical guideline on the diagnosis and management of suspected idiopathic pulmonary fibrosis.'

3 Clinical need for the guideline

3.1 Epidemiology

a) Idiopathic pulmonary fibrosis (IPF) used to be called cryptogenic fibrosing alveolitis. It is a severe progressive lung disease, in which fibrous tissue forms in the lungs. Smoking is believed to be a risk-factor but the exact cause is unknown.

b) Most people with idiopathic pulmonary fibrosis experience worsening breathlessness leading to respiratory failure. Average survival is around 3 years, and mortality rates are comparable to many solid cancers.

c) The median age of presentation is 70 years. It is rare in people younger than 45.

d) Idiopathic pulmonary fibrosis is becoming more common. The incidence is around eight to nine per 100,000 person years, which

means more than 4000 new cases occur in the UK each year. The prevalence is around 15 to 25 per 100,000 and increases with age. The average hospital with a catchment of 500,000 will have 35 new cases a year and the average GP surgery of 10,000 patients will have two new cases every 3 years.

3.2 Current practice

a) Idiopathic pulmonary fibrosis is one of several interstitial lung diseases that tend to present in a similar manner with breathlessness, bibasal chest crepitations and diffuse chest X-ray changes. Idiopathic pulmonary fibrosis has the poorest prognosis of these disorders, so establishing a timely, confident diagnosis is important. A confident diagnosis needs careful integration of clinical, radiological (high-resolution CT scans) and pathological data and there is evidence that this is best achieved in a specialist multidisciplinary setting.

b) To manage IPF, there is evidence to support a role for some types of best supportive care, such as smoking cessation, pulmonary rehabilitation, withdrawal of ineffective therapy, oxygen therapy and palliation of symptoms.

c) Currently, there is no proven effective drug therapy for IPF. Corticosteroids and azathioprine are often used. A recent trial suggests the addition of N-acetylcysteine to prednisilone and azathioprine may slow the rate of disease progression more than prednisolone and azathioprine alone.

d) There are some emerging therapies for the disease. Some of these are costly, and all are as yet unproven but they may change the treatment landscape.

e) Lung transplantation is a valuable resource for selected patients. It is suitable for only a minority of patients with idiopathic pulmonary fibrosis, and the number of patients that die waiting for a lung

transplant is proportionately higher than any other patient group. Efforts should be made to identify which patients would benefit most.

f) Access to pulmonary rehabilitation services and palliative care for idiopathic pulmonary fibrosis is not uniform. The past few years have seen several ad hoc specialist centres emerge, often with limited or no resource support.

g) The British Thoracic Society guidelines were published in 2008. There is an urgent need for guidance on initial diagnosis and the management of idiopathic pulmonary fibrosis because the ongoing burden of disease has significant resource implications, and because of the imminent emergence of new potential therapies.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults (18 and older) with suspected or diagnosed idiopathic pulmonary fibrosis.

b) No patient subgroups have been identified as needing specific consideration.

4.1.2 Groups that will not be covered

a) Children and young people (younger than 18).

b) People with a diagnosis of pulmonary fibrosis as a complication of:

- connective tissue disorders (for example, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, polymyositis and dermatomyositis)
- a known exogenous agent (for example, drug-induced disease or asbestosis).

4.2 Healthcare setting

All healthcare settings.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) Diagnosis:

- high resolution computed tomography (CT) scanning
- biopsy (bronchoalveolar lavage and surgical lung biopsy)
- multidisciplinary teams to achieve a consensus diagnosis
- pulmonary function tests.

b) Prognosis:

- pulmonary function tests (resting spirometric and gas transfer measurement)
- sub-maximal exercise testing
- echocardiography.

c) Treatment of the disease with the following drugs:

- prednisolone
- mycophenolate mofetil
- warfarin

- azathioprine
- N-acetyl cysteine
- proton-pump inhibitors
- co-trimoxazole
- ambrisentan
- bosanten
- sildenafil.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform the decisions they make with patients.

d) Symptom relief:

- lung transplantation timing and referral
- best supportive care (benzodiazepines, oxygen therapy and palliative care)
- non invasive and invasive ventilation
- pulmonary rehabilitation (breathlessness management).

e) Patient review and follow-up.

4.3.2 Clinical issues that will not be covered

a) Therapies for pulmonary hypertension as a complication of idiopathic pulmonary fibrosis.

b) Treatment of lung cancer as a complication of idiopathic pulmonary fibrosis.

c) Lung transplantation, other than timing and referral.

4.4 Main outcomes

a) Lung capacity: measurement of vital capacity (VC) or forced vital capacity (FVC).

b) Gas transfer: measurement of the carbon monoxide diffusing capacity of the lungs (T_LCO).

c) Change in health-related quality of life measured using the Short Form-36 or Saint George's Respiratory Questionnaire and/or a measure of function such as the 6 minute walk test or EQ 5D.

d) Hospitalisations due to exacerbation of the disease.

e) Mortality.

f) Adverse events.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in September 2011.

5 Related NICE guidance

5.1 Published guidance

- Lung cancer. NICE clinical guideline 121 (2011). Available from www.nice.org.uk/guidance/CG121
- Tuberculosis. NICE clinical guideline 117 (2011). Available from www.nice.org.uk/guidance/CG117
- Chronic obstructive pulmonary disease. NICE clinical guideline 101 (2010). Available from www.nice.org.uk/guidance/CG101
- Smoking cessation services. NICE public health guidance 10 (2008). Available from www.nice.org.uk/guidance/PH10.

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website).

- Opioids in palliative care. NICE clinical guideline. Publication expected May 2012.

5.2.1 NICE guidance to be incorporated

This guideline is intended to incorporate the following NICE guidance, subject to a technology appraisal consultation:

- Pirfenidone for the treatment of idiopathic pulmonary fibrosis. NICE technology appraisal. Publication date to be confirmed.

6 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the

Appendix B: Declarations of interest

B.1 Dr Nik Hirani

GDG meeting	Declaration of Interests	Actions taken
On Application	NH declared he knew of no personal pecuniary interests or personal family interests in the past 12 months and had nothing to declare for the upcoming month. NH declared non-personal pecuniary interests, which led to payments made directly to the University of Edinburgh: NH received a non-commercial clinician scientist fellowship to study mechanisms of acute lung injury and repair. Funded by GlaxoSmithKlein from 2001to 2005. NH was the principal investigator for local site in a multiple-centre phase 3 clinical trial of endothelin antagonist in IPF (ARTEMIS) study. Funded by Gilead, from 2010 to Dec 2011. NH was the principal investigator in MRC/Industry-funded phase 1/2 clinical trial of CDK inhibitor. Funded by Astex, from 2010/2011 to January 2012. NH was the principal investigator in collaborative research on pre-clinical models of lung injury and fibrosis. Funded by AstraZeneca, from 2010 to December 2011. NH is the principal investigator for an MRC funded molecular imaging study in pulmonary fibrosis in partnership with AstraZeneca, which is due to commence in 2013. NH declared personal non-pecuniary interests. NH is a member of the British Thoracic Society and Chair of ILD specialist advisory group. NH also belongs to the Advisory board EurlPFnet (European Registry of IPF).	None
First GDG meeting (16/09/2011)	NH had no new interests to declare other than those declared at upon application to the GDG.	None
Second GDG Meeting (21/10/11)	NH had no new interests to declare.	None
Third GDG Meeting (02/12/11)	NH declared a non-personal pecuniary interest. NH attended a BTS meeting and gave a presentation on IPF. Travel and accommodation was provided for by the University of Edinburgh.	None
Fourth GDG Meeting (12/01/12)	NH had no new interests to declare.	None
Fifth GDG Meeting (24/02/12)	NH had no new interests to declare.	None

GDG meeting	Declaration of Interests	Actions taken
Sixth GDG Meeting (28/03/12)	NH declared a personal pecuniary interest. NH gave a presentation at the April 2012 Keystones Lung Fibrosis meeting, for which he received travel and accommodation expenses from the University of Edinburgh.	None
Seventh GDG Meeting (11/05/12)	NH declared a non-personal pecuniary interest. NH is the principal investigator for an MRC funded molecular imaging study in pulmonary fibrosis in partnership with AstraZeneca, which is due to commence in July 2013. Funding is paid directly to the University of Edinburgh: NH was been Approached in the last month by Intermune to sit on an advisory board for the Passport study, which is a patient named surveillance study of those on Pirfenidone, which he declined.	None
Eighth GDG Meeting (21/06/12)	NH had no new interests to declare.	None
Ninth GDG Meeting (25/07/12)	NH declared a personal non-pecuniary interest. NH will be an adviser on the NIHR HTA report, which is evaluating the clinical and cost effectiveness of treatments for idiopathic pulmonary fibrosis. This systematic review is due for completion in spring 2013.	None
Tenth GDG Meeting (07/09/12)	NH declared personal non-pecuniary interests. NH is a member of the BTS steering group developing an IPF National Registry for which he receives no funding. A student which NH supervises received funding from Boehringer Ingelheim to attend the ERS conference. Funding was within reasonable limits for conference attendance. NH also endorsed an article in Thorax, which discussed what outcomes should be used as end points in trials in lung fibrosis. NH did not receive any funding for this endorsement.	None
Eleventh GDG Meeting (05/10/12)	NH declared a personal non-pecuniary interest. NH attended an IPF meeting, ICLAF, in Italy, from the 29th September to 4th October 2012. NH also published an abstract in the ERS journal. No financial remuneration was received for either of these declarations.	None
Twelfth GDG Meeting (01/11/12)	NH had no new interests to declare.	None
Thirteenth GDG Meeting (06/03/13)	NH had no new interests to declare.	None

B.2 Angela Key

GDG meeting	Declaration of Interests	Actions taken
On Application	AK declared she knew of no personal pecuniary, personal family,	None

GDG meeting	Declaration of Interests	Actions taken
	non-personal pecuniary or personal non-pecuniary interests in the previous 12 months or upcoming month.	
First GDG meeting (16/09/2011)	AK had no new interests to declare other than those declared at upon application to the GDG.	None
Second GDG Meeting (21/10/11)	AK had no new interests to declare.	None
Third GDG Meeting (02/12/11)	AK had no new interests to declare.	None
Fourth GDG Meeting (12/01/12)	AK had no new interests to declare.	None
Fifth GDG Meeting (24/02/12)	Did not attend.	None
Sixth GDG Meeting (28/03/12)	AK had no new interests to declare.	None
Seventh GDG Meeting (11/05/12)	AK had no new interests to declare.	None
Eighth GDG Meeting (21/06/12)	AK had no new interests to declare.	None
Ninth GDG Meeting (25/07/12)	AK had no new interests to declare.	None
Tenth GDG Meeting (07/09/12)	AK had no new interests to declare.	None
Eleventh GDG Meeting (05/10/12)	AK had no new interests to declare	None
Twelfth GDG Meeting (01/11/12)	Did not attend.	None
Thirteenth GDG Meeting (06/03/13)	AK had no new interests to declare.	None

B.3 Ann Millar

GDG meeting	Declaration of Interests	Actions taken
On Application	AM declared she knew of no personal pecuniary or personal family interests in the previous 12 months or upcoming month. AM declared a non-personal pecuniary interest. AM is involved with trials of drug therapies for patients with IPF as recommended by the British Thoracic Society guidelines. These trials are funded by Boehringer Ingelheim and funding goes into a respiratory departmental research fund (on-going). AM declared personal non-pecuniary interests. AM is the Chairman of the British Association for Lung Research and member of the Respiratory Expert Advisory Group for the MHRA (2009-2013.	None
First GDG meeting (16/09/2011)	AM had no new interests to declare other than those declared at upon application to the GDG.	None
Second GDG Meeting (21/10/11)	Did not attend.	None
Third GDG Meeting (02/12/11)	Ann Millar declared she had written an editorial for the Thoracic Society on the PANTHER study.	None
Fourth GDG Meeting (12/01/12)	AM had no new interests to declare.	None
Fifth GDG Meeting (24/02/12)	AM had no new interests to declare.	None
Sixth GDG Meeting (28/03/12)	AM had no new interests to declare.	None
Seventh GDG Meeting (11/05/12)	AM had no new interests to declare.	None
Eighth GDG Meeting (21/06/12)	Did not attend.	None
Ninth GDG Meeting (25/07/12)	AM had no new interests to declare.	None
Tenth GDG Meeting (07/09/12)	AM declared a personal non-pecuniary interest. AM is a member of the BTS steering group developing an IPF National Registry, for which she receives no funding.	None
Eleventh GDG Meeting (05/10/12)	AM had no new interests to declare.	None

GDG meeting	Declaration of Interests	Actions taken
Twelfth GDG Meeting (01/11/12)	AM had no new interests to declare.	None
Thirteenth GDG Meeting (06/03/13)	AM had no new interests to declare.	None

B.4 Annette Duck

GDG meeting	Declaration of Interests	Actions taken
On Application	AD declared she knew of no personal pecuniary, personal family or personal non-pecuniary interests in the previous 12 months or upcoming month. AD declared non-personal pecuniary interests. AD has been the research nurse and clinical trial co-ordinator in trials associated with Intermune, Actelion, Boehringer Ingelheim and Gilead. AD is a committee member and Chair of the Association of Respiratory Nurse Specialists (ARNS), she has had associations and negotiated sponsorship on behalf of the association with Astra Zeneca, Boehringer Ingelheim, GSK, Chiesi, Nycomed, MSD, Nutricia, Teva, Actelion, Orion and Pfizer. This funding has supported educational annual conferences, study days, courses, and the secretariat and 10 committee expenses to run the association. AD's term of office ended in July 2011.	None
First GDG meeting (16/09/2011)	AD had no new interests to declare other than those declared at upon application to the GDG.	None
Second GDG Meeting (21/10/11)	Did not attend.	None
Third GDG Meeting (02/12/11)	AD declared she had attended an IPF meeting in Berlin and had also been involved in discussions to set up an IPF patient support group in the previous month, both funded for by Intermune. AD also informed the group that her current employment in the NHS was under review and due to this she had also been in discussions with Intermune regarding future employment possibilities, but no further developments had yet been made.	None
Fourth GDG Meeting (12/01/12)	Did not attend.	None
Fifth GDG Meeting (24/02/12)	Annette Duck declared a personal non-pecuniary interest that she had attended two IPF patient support group meetings since the last GDG meeting. No financial re-numerations were received for either	None

GDG meeting	Declaration of Interests	Actions taken
	of these days.	
Sixth GDG Meeting (28/03/12)	AD declared non-personal pecuniary interests. AD was involved in developing and speaking at a patient support group meeting on the 10th March 2012 and the 25th April at the BLF NW ILD networking day. No financial re-numerations were received for either of these days.	None
Seventh GDG Meeting (11/05/12)	AD declared a personal pecuniary interest. AD acted as a freelance trainer on the ARNS End of Life course in Swansea 19th and 20th April 2012, for which she received £300.00 per day. AD also declared personal non-pecuniary interests. AD was a speaker at the North-West BLF ILD/IPF networking patient support group meeting on the 25th April. Ad also presented at the International Primary Care Respiratory Society Conference in Edinburgh on the 28th April. No financial re-numerations were received for either of these days.	None
Eighth GDG Meeting (21/06/12)	AD declared a personal pecuniary interest. AD acted as a freelance trainer on the ARNS End of Life care in Cambridge in May, for which she received £300 per day.	None
Ninth GDG Meeting (25/07/12)	AD declared a personal pecuniary interest for consulting at an IPF patient support day organised by Intermune on the 19th July 2012, for which she received a fee of £225. Intermune manufactures Pirfenidone, which is not a drug highlighted in the scope of this guideline. AD also declared non-personal pecuniary interests. AD attended a meeting to develop a national IPF support group in Nottingham on 20th July 2012 outside of her NHS commitments. No expenses or reimbursement was received for attending this meeting. AD is also a co-author on two articles, one on the benefits of a MDT in ILD diagnosis and another on the benefits of ambulatory oxygen in IPF, which have both been submitted to the European Respiratory Journal.	None
Tenth GDG Meeting (07/09/12)	AD declared personal non-pecuniary interests. AD attended a study day organised by Intermune on 28th June. She received no financial remuneration for attendance. AD also presented a research poster at the ERS on 4th September on 'Perceptions, experiences and information needs of patients with IPF'. The department in which AD works is taking part in the Pirfenidone Named Patient Programme, which commenced in September 2011 and for which there is no funding. AD declared a personal pecuniary interest that her hotel accommodation at the ERS was sponsored by Intermune. Her flight expenses were covered by her institution.	None
Eleventh GDG Meeting (05/10/12)	AD declared personal pecuniary interests. AD acted as a freelance trainer on the ARNS ILD study day in Belfast for which she received trainer fee of £300.00. AD was also involved in a radio interview on South Manchester radio for which there was no financial renumeration. AD declared a personal non-pecuniary interest, as she was involved with IPF awareness week sponsored by Intermune. Intermune sponsored activities at UHSM that were	None

GDG meeting	Declaration of Interests	Actions taken
	associated with IPF Awareness week with £500.	
Twelfth GDG Meeting (01/11/12)	Did not attend	None
Thirteenth GDG Meeting (06/03/13)	AD declared personal pecuniary interests. AD acted as a freelance trainer for the ARNS 2-day end of life course in Cheltenham in November 2012, in Belfast in January 2013 and in Colchester in March 2013. AD also ran an ARNS ILD study day in Manchester and a BOC ILD oxygen talk in November 2012. AD received a fee for all of the training and study days she was involved with and all were deemed within reasonable limits. AD declared personal non-pecuniary interests. AD was a co-author on two abstracts, one titled 'real life experience of using pirfenidone' and another on the quality of life in patients using pirfenidone. Both abstracts were submitted to the BTS.	None

B.5 Geraldine Burge

GDG meeting	Declaration of Interests	Actions taken
On Application	GB declared she knew of no personal pecuniary or personal family interests in the previous 12 months or upcoming month. GB declared the following non-personal pecuniary interests. GB is involved with drug studies conducted at Birmingham NHS hospital; Inspire Study Gamma Interferon/ placebo in patients with UIP, funded by Intermune was completed in 2010; Capacity Study Pirfenidone /placebo in patients with UIP, funded by Intermune started in 2007; Recap study open labelled Pirfenidone , funded by Intermune; and Tomorrow Study Vargate/ Placebo in pts with UIP, funded by Boeringher and Ingleheim, started in 2009. All of these studies have now come to an end in 2012. All funding goes to the Medical Innovations research unit at the Birmingham Heartlands hospital (MIDRU). GB declared a personal family interest, as her husband is the principle investigator of all the above studies mentioned since 2003 to 2012.	
First GDG meeting (16/09/2011)	GB had no new interests to declare other than those declared at upon application to the GDG.	None
Second GDG Meeting (21/10/11)	GB declared a personal family interest that her husband is the principle investigator of all the IPF studies she has been involved with since 2003, which includes involvement with Pirfenedone, Vargate and Gamma interferone. GB also declared personal non-pecuniary interests. GB	None

GDG meeting	Declaration of Interests	Actions taken
	attended two IPF meetings sponsored by Boeringher Ingleheim and one by Intermune at the ERS in September. GB also attended a Patient Group Advisory Panel in Manchester, organised by WG Consulting. GB is also due to give a lecture to regional physiotherapist on IPF in the upcoming month.	
Third GDG Meeting (02/12/11)	GB declared a personal pecuniary interest that she had attended an IPF meeting in Berlin during the previous month, for which travel and accommodation was funded by Intermune.	None
Fourth GDG Meeting (12/01/12)	Did not attend.	None
Fifth GDG Meeting (24/02/12)	GB declared a personal non-pecuniary interest that she had attended an IPF patient support group since the last GDG meeting.	None
Sixth GDG Meeting (28/03/12)	Did not attend.	None
Seventh GDG Meeting (11/05/12)	GB declared non-personal pecuniary interests. GB attended an ERS school meeting on the 4th May, for which she received travel and accommodation expenses. GB also attended a non-IPF related ARS conference funded by GlaxoSmithKlein, for which she received £300 to attend. GB also declared a personal non-pecuniary interest. GB declared a personal non-pecuniary interest, as she attended an IPF support group meeting in Nottingham on the 10th March 2012, for which no funding was received.	None
Eighth GDG Meeting (21/06/12)	GB had no new interests to declare.	None
Ninth GDG Meeting (25/07/12)	Did not attend.	None
Tenth GDG Meeting (07/09/12)	GB declared personal non-pecuniary interests. GB attended an IPF update in June, for which she received no funding and has also been involved with an IPF patient self-help group (query funding). She also attended an ERS conference, for which travel and accommodation was funded for by Intermune. All expenses were within reasonable limits.	None
Eleventh GDG Meeting (05/10/12)	Did not attend.	None
Twelfth GDG Meeting (01/11/12)	Did not attend.	None
Thirteenth GDG	GB declared personal pecuniary interests. GB was involved in a	None

GDG meeting	Declaration of Interests	Actions taken
meeting (06/03/13)	teaching course sponsored by ARNS in September 2012, for which travel and accommodation was funded for. She attended an ARNS 2-day end of life course in Cheltenham in November 2012, for which only accommodation was paid for. GB also attended the AIRS education meeting in Rome in November 2012, for which flights, meals and accommodation for one night was paid for. Registration was funded by GB's work for approximately £800. GB will also be teaching at the Brompton at the end of April 2013, but will not be receiving any fees for this, only travel fares.	

B.6 Malcolm Weallans

GDG meeting	Declaration of Interests	Actions taken
On Application	MW declared he knew of no personal pecuniary interests, personal family or non-personal pecuniary interests in the past 12 months and had nothing to declare for the upcoming month. MW declared a personal non-pecuniary interest. MW contributes to the UK yahoo self-help group pulmonaryfibrosis@yahoogroups.com and is the founder of the Crackle Fund, which raises funds for BLF.	None
First GDG meeting (16/09/2011)	MW had no new interests to declare other than those declared at upon application to the GDG.	None
Second GDG Meeting (21/10/11)	MW had no new interests to declare.	None
Third GDG Meeting (02/12/11)	MW had no new interests to declare.	None
Fourth GDG Meeting (12/01/12)	MW declared that since the last GDG meeting he has become an honorary treasurer for the IPF Trust.	None
Fifth GDG Meeting (24/02/12)	MW had no new interests to declare.	None
Sixth GDG Meeting (28/03/12)	MW declared a new personal non-pecuniary interest. MW attended an IPF patient support group in Nottingham in March 2012. No sponsorship was received for this.	None
Seventh GDG Meeting (11/05/12)	MW had no new interests to declare.	None
Eighth GDG	Did not attend	None

GDG meeting	Declaration of Interests	Actions taken
Meeting (21/06/12)		
Ninth GDG Meeting (25/07/12)	MW had no new interests to declare.	None
Tenth GDG Meeting (07/09/12)	MW had no new interests to declare.	None
Eleventh GDG Meeting (05/10/12)	MW declared a personal non-pecuniary interest. MW is attending a research day at the Brompton, which is funded by Intermune, but for which MW does receive any financial remuneration. MW is also attending the Pirfenidone technology appraisal meeting in Manchester on the 24th October, for which travel expenses are funded by NICE.	None
Twelfth GDG Meeting (01/11/12)	MW had no new interests to declare.	None
Thirteenth GDG Meeting (06/03/13)	MW declared a personal pecuniary interest. He will be giving a presentation on IPF at the East Anglian University in April, for which travel expenses will be received.	None

B.7 Melissa Hippard

GDG meeting	Declaration of Interests	Actions taken
On Application	MH declared she knew of no personal pecuniary interests, personal family or non-personal pecuniary interests in the past 12 months and had nothing to declare for the upcoming month. MH declared personal non-pecuniary interests. MH is a member of an online support group: (http://health.groups.yahoo.com/group/pulmonaryfibrosis/) and has also posted in the past on other support groups: Huf'n'Puf (US group), PF Facebook group and the BLF support group. MH has attended the launch of and given donations to 'Breathing Matters' a charity set up to raise funds for research at the Centre for Respiratory Research, UCLH.	None
First GDG meeting (16/09/2011)	Did not attend.	None
Second GDG Meeting (21/10/11)	MH had no new interests to declare.	None
Third GDG Meeting	MH had no new interests to declare.	None

GDG meeting	Declaration of Interests	Actions taken
(02/12/11)		
Fourth GDG Meeting (12/01/12)	MH had no new interests to declare.	None
Fifth GDG Meeting (24/02/12)	MH had no new interests to declare.	None
Sixth GDG Meeting (28/03/12)	MH had no new interests to declare.	None
Seventh GDG Meeting (11/05/12)	MH had no new interests to declare.	None
Eighth GDG Meeting (21/06/12)	Did not attend.	None
Ninth GDG Meeting (25/07/12)	MH had no new interests to declare.	None
Tenth GDG Meeting (07/09/12)	MH declared a personal non-pecuniary interest that she has volunteered to be a patient expert on the Pirfenidone technology appraisal committee, due to take place in October 2012.	None
Eleventh GDG Meeting (05/10/12)	Did not attend	None
Twelfth GDG Meeting (01/11/12)	MH had no new interests to declare.	None
Thirteenth GDG Meeting (06/03/13)	MH declared a personal non-pecuniary interest. She was interviewed by Intermune to discuss the impact of IPF on her lifestyle and family. No fee was received.	None

B.8 Nicholas Kim Harrison

GDG meeting	Declaration of Interests	Actions taken
On Application	NKH declared he knew of no personal pecuniary interests or non-personal pecuniary interests in the past 12 months and had nothing to declare for the upcoming month. NKH declared a personal family interest. NKH's wife is an Assistant Medical Director (Primary Care) for Abertawe Bro Morgannwg University Health Board and is lead for the development of 'Care Pathways' (from 2010 to present).	None

GDG meeting	Declaration of Interests	Actions taken
	NKH declared personal pecuniary interests. NKH is the Lead for 'Lung Research Wales'. NKH was the Chairman of the British Association for Lung Research from 2005 to 2009 and stepped down as a member of the BALR Committee in 2011. NKH represents Wales on the UK Respiratory Research Collaborative as well as the Respiratory Specialty Group of the National Institute for Health Research (NIHR) Clinical Research Network (from 2005 to present). NKH enrolled patients into the following clinical trial: TIPAC (Treating Interstitial Pneumonia with the Addition of Co-Trimoxazole) – a phase III interventional study (funded by the NIHR Research for Patient Benefit and the East Anglia Thoracic Society and sponsored by the University of East Anglia). This study closed 31st December 2009 NKH enrolled patients into the following observational cohort study: Trent Lung Fibrosis Study – Does the presence of thrombophilia increase the risk of developing idiopathic pulmonary fibrosis? (Funded by the MRC and sponsored by the University of Nottingham, from 2009-2011).	
First GDG meeting (16/09/2011)	NKH had no new interests to declare other than those declared at upon application to the GDG.	None
Second GDG Meeting (21/10/11)	NKH had no new interests to declare.	None
Third GDG Meeting (02/12/11)	NKH had no new interests to declare.	None
Fourth GDG Meeting (12/01/12)	NKH had no new interests to declare.	None
Fifth GDG Meeting (24/02/12)	NKH had no new interests to declare.	None
Sixth GDG Meeting (28/03/12)	NKH had no new interests to declare.	None
Seventh GDG Meeting (11/05/12)	NKH had no new interests to declare.	None
Eighth GDG Meeting (21/06/12)	NKH declared a non-personal pecuniary interest. NKH will be a co-investigator on a trial investigating the end of life needs of patients with IPF and their carers due to commence later in 2012 (date to be confirmed). The trial is funded by the Marie Curie Research Programme, and payment goes to a Palliative Care hospital.	None
Ninth GDG Meeting	NKH had no new interests to declare.	None

GDG meeting	Declaration of Interests	Actions taken
(25/07/12)		
Tenth GDG Meeting (07/09/12)	NKH declared a person non-pecuniary interest as he has endorsed and article in Thorax, which discussed what outcomes should be used as end points in trials in lung fibrosis. NKH did not receive any funding for this endorsement.	None
Eleventh GDG Meeting (05/10/12)	NKH had no new interests to declare.	None
Twelfth GDG Meeting (01/11/12)	NKH had no new interests to declare.	None
Thirteenth GDG Meeting (06/03/13)	Did not attend.	None

B.9 Nicholas Screaton

GDG meeting	Declaration of Interests	Actions taken
On Application	NS declared personal pecuniary interests. NS has been involved in ethics submission for trials regarding ionising radiation. NS has received a payment of £300 from Actelion to cover expenses when delivering a lecture on imaging at a 'The Midlands Pulmonary Hypertension Forum'. NS declared he knew of no personal family interests in the previous 12 months or upcoming month. NS declared non-personal pecuniary interests. NS is the president of the British Society of Thoracic Imaging, where financial support is gained from electrical companies. NS declared personal non-pecuniary interests. NS has published on PET-CT evaluation of interstitial lung disease as well as HRCT in the follow-up of NSIP.	None
First GDG meeting (16/09/2011)	Did not attend	None
Second GDG Meeting (21/10/11)	NS had no new interests to declare.	None
Third GDG Meeting (02/12/11)	NS had no new interests to declare.	None
Fourth GDG	NS had no new interests to declare.	None

GDG meeting	Declaration of Interests	Actions taken
Meeting (12/01/12)		
Fifth GDG Meeting (24/02/12)	NS had no new interests to declare.	None
Sixth GDG Meeting (28/03/12)	Did not attend	None
Seventh GDG Meeting (11/05/12)	NS had no new interests to declare.	None
Eighth GDG Meeting (21/06/12)	Did not attend	None
Ninth GDG Meeting (25/07/12)	NS had no new interests to declare.	None
Tenth GDG Meeting (07/09/12)	NS declared a non-personal non-pecuniary interest. His department has received funding from GlaxoSmithKlein for one radiologist and one physicist positions.	None
Eleventh GDG Meeting (05/10/12)	Did not attend	None
Twelfth GDG Meeting (01/11/12)	Did not attend	None
Thirteenth GDG Meeting (06/03/13)	NS had no new interests to declare.	None

B.10 Patrick Wilson

GDG meeting	Declaration of Interests	Actions taken
On Application	PW declared he knew of no personal pecuniary, personal family or non-personal pecuniary interests in the previous 12 months or upcoming month. PW declared person non-pecuniary interests. PW has contributed to NICE scoping workshops involving inhaled mannitol and dry powder colistimethate sodium in cystic fibrosis. PW is involved though the United Kingdom Clinical Pharmacy Association in using web-based technology to deliver continuing education to pharmacists in the area of respiratory medicine.	None
First GDG	PW had no new interests to declare other than those declared at	None

GDG meeting	Declaration of Interests	Actions taken
meeting (16/09/2011)	upon application to the GDG.	
Second GDG Meeting (21/10/11)	PW had no new interests to declare.	None
Third GDG Meeting (02/12/11)	PW had no new interests to declare.	None
Fourth GDG Meeting (12/01/12)	PW had no new interests to declare.	None
Fifth GDG Meeting (24/02/12)	PW had no new interests to declare.	None
Sixth GDG Meeting (28/03/12)	Did not attend.	None
Seventh GDG Meeting (11/05/12)	PW had no new interests to declare.	None
Eighth GDG Meeting (21/06/12)	PW had no new interests to declare	None
Ninth GDG Meeting (25/07/12)	PW had no new interests to declare	None
Tenth GDG Meeting (07/09/12)	PW declared a non-personal pecuniary interest. PW has successfully applied for a Gilead Fellowship Grant to carry out a research project into improving adherence with nebulised antibiotic therapy in cystic fibrosis. This grant totals £10 000 and is to be paid directly into a departmental account on which PW is not named.	None
Eleventh GDG Meeting (05/10/12)	PW declared a personal pecuniary interest. PW attended training on "Negotiating and Influencing", which was paid for by Bayer Pharmaceuticals.	None
Twelfth GDG Meeting (01/11/12)	Did not attend.	None
Thirteenth GDG Meeting (06/03/13)	PW declared a personal pecuniary interest. He attended a training day discussing inhalers, funded by his department.	None

B.11 Richard Hubbard

GDG meeting	Declaration of Interests	Actions taken

GDG meeting	Declaration of Interests	Actions taken
On Application	RH declared he knew of no personal family interests in the previous 12 months or upcoming month. RH declared personal pecuniary interests. In October 2009 RH received approximately £300 for consulting on a GSK design of a cohort study and ceased being an editor at Thorax in 2010. RH declared non-personal pecuniary interests. RH is a co-applicant on a joint research grant from GSK for £800,000 to study biomarkers for people with IPF (2009-2011). RH is the principle investigator on an MRC grant which is currently investigating the aetiology of Idiopathic pulmonary fibrosis in the East Midlands (2009-August 2012). RH is currently the British Lung Foundation Professor of Epidemiology and receives £85,000 per year research funding as part of this role (term due to end in 2016). RH declared personal non-pecuniary interests. RH is a committee member of a local Breathe Easy group. RH is a member of the British Lung Foundation Scientific Committee (term due to end 2016). RH was a member of the British Thoracic Society guidelines on Interstitial Lung disease.	None
First GDG meeting (16/09/2011)	Did not attend.	None
Second GDG Meeting (21/10/11)	RH declared that his department had been given a grant from MRC to study the natural history and aetiology of IPF. He is also part of a consortium on biomarkers for IPF for GSK.	None
Third GDG Meeting (02/12/11)	Did not attend.	None
Fourth GDG Meeting (12/01/12)	Did not attend.	None
Fifth GDG Meeting (24/02/12)	Did not attend.	None
Sixth GDG Meeting (28/03/12)	RH had no new interests to declare.	None
Seventh GDG Meeting (11/05/12)	RH had no new interests to declare.	None
Eighth GDG Meeting (21/06/12)	Did not attend.	None
Ninth GDG Meeting	RH had no new interests to declare.	None

GDG meeting	Declaration of Interests	Actions taken
(25/07/12)		
Tenth GDG Meeting (07/09/12)	Did not attend.	None
Eleventh GDG Meeting (05/10/12)	RH declared non-personal pecuniary interests. RH's department has been awarded a grant (£150,000) by the Roy Castle Lung Cancer Foundation to found a research fellowship into delivery of care for people with lung cancer. RH also declared that he is a collaborator on a research project into palliative care aspects of Idiopathic Pulmonary Fibrosis. The main lead for the grant is University of Cardiff	None
Twelfth GDG Meeting (01/11/12)	RH had no new interests to declare.	None
Thirteenth GDG Meeting (06/03/13)	RH had no new interests to declare.	None

B.12 Susan Copley

GDG meeting	Declaration of Interests	Actions taken
On Application	SC declared she knew of no personal pecuniary, personal family or non-personal pecuniary interests in the previous 12 months or upcoming month. SC declared a personal non-pecuniary interest. SC has been involved with Research projects in the radiological diagnosis of the condition as a scorer of CT scans.	None
First GDG meeting (16/09/2011)	SC had no new interests to declare other than those declared at upon application to the GDG.	None
Second GDG Meeting (21/10/11)	Did not attend.	None
Third GDG Meeting (02/12/11)	Did not attend.	None
Fourth GDG Meeting (12/01/12)	SC had no new interests to declare.	None
Fifth GDG Meeting (24/02/12)	SC had no new interests to declare.	None

GDG meeting	Declaration of Interests	Actions taken
Sixth GDG Meeting (28/03/12)	Did not attend.	None
Seventh GDG Meeting (11/05/12)	SC had no new interests to declare.	None
Eighth GDG Meeting (21/06/12)	SC had no new interests to declare.	None
Ninth GDG Meeting (25/07/12)	SC had no new interests to declare.	None
Tenth GDG Meeting (07/09/12)	SC declared personal non-pecuniary interests. SC is a member of the BTS steering group developing an IPF National Registry, for which no funding is received, and is also a co-organizer of an ILD Educational Course, NHLI, which commenced in March 2013 and the funding goes to her department.	None
Eleventh GDG Meeting (05/10/12)	Did not attend.	None
Twelfth GDG Meeting (01/11/12)	SC had no new interests to declare.	None
Thirteenth GDG Meeting (06/03/13)	SC had no new interests to declare.	None

B.13 Tessa Lewis

GDG meeting	Declaration of Interests	Actions taken
On Application	TL declared she knew of no personal pecuniary, personal family, non-personal pecuniary or personal non-pecuniary interests in the previous 12 months or upcoming month.	None
First GDG meeting (16/09/2011)	TL had no new interests to declare other than those declared at upon application to the GDG.	None
Second GDG Meeting (21/10/11)	TL had no new interests to declare.	None
Third GDG Meeting (02/12/11)	TL had no new interests to declare.	None
Fourth GDG	TL had no new interests to declare.	None

GDG meeting	Declaration of Interests	Actions taken
Meeting (12/01/12)		
Fifth GDG Meeting (24/02/12)	TL had no new interests to declare.	None
Sixth GDG Meeting (28/03/12)	TL had no new interests to declare.	None
Seventh GDG Meeting (11/05/12)	TL had no new interests to declare.	None
Eighth GDG Meeting (21/06/12)	TL had no new interests to declare.	None
Ninth GDG Meeting (25/07/12)	Did not attend.	None
Tenth GDG Meeting (07/09/12)	TL had no new interests to declare.	None
Eleventh GDG Meeting (05/10/12)	TL had no new interests to declare.	None
Twelfth GDG Meeting (01/11/12)	Did not attend.	None
Thirteenth GDG Meeting (06/03/13)	TL had no new interests to declare.	None

B.14 Prof Andrew G Nicholson – co-opted expert

GDG meeting	Declaration of Interests	Actions
On Application	AGN declared personal pecuniary interests. AGN has received consultancy fees from Actelion Ltd, Boehringer Ingelheim Ltd, Intermune Ltd for involvement with drug trials for idiopathic pulmonary fibrosis in the past 10 years.	None
Fourth GDG meeting (12/01/2012)	AGN declared no new interests to those declared upon application.	None
Fifth GDG Meeting (24/02/2012)	AGN declared no new interests to those declared upon application.	None

B.15 Mr Stephen Clark – co-opted expert

GDG meeting	Declaration of Interests	Actions
On Application	SC declared he had no conflicts of interests in the previous 12 months or upcoming month.	None
Tenth GDG Meeting (07/09/12)	SC declared no new interests to those declared upon application.	None

B.16 Professor Sally Singh – co-opted expert

GDG meeting	Declaration of Interests	Actions
On Application	SS declared she had no conflicts of interests in the previous 12 months or upcoming month.	None
Third GDG Meeting (02/12/2011)	SS declared no new interests to those declared upon application.	None
Ninth GDG Meeting (25/07/12)	SS declared a personal non-pecuniary interest. She will be an adviser on the NIHR HTA report, which is evaluating the clinical and cost effectiveness of treatments for idiopathic pulmonary fibrosis. This systematic review is due for completion in spring 2013.	None

B.17 NCGC technical team

GDG meeting	Declaration of Interests of the NCGC members	Actions
First GDG meeting (16/09/2011)	No member of the NCGC knew of a personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.	None
Second GDG Meeting (21/10/2011)	No interests to declare.	None
Third GDG Meeting (02/12/2011)	No interests to declare.	None
Fourth GDG Meeting (12/01/2012)	No interests to declare.	None
Fifth GDG	No interests to declare.	None

GDG meeting	Declaration of Interests of the NCGC members	Actions
Meeting (24/02/2012)		
Sixth GDG Meeting (28/03/2012)	No interests to declare.	None
Seventh GDG Meeting (11/05/2012)	No interests to declare.	None
Eight GDG Meeting (21/06/12)	VDN declared a non-personal pecuniary interest. VDN will be attending a meeting in St Petersburg, for which travel and accommodation is being funded by Pfizer. Consultancy fee will be paid into the NCGC account. Pfizer does not manufacture any IPF related drugs. No other NCGC member had any interests to declare.	None
Ninth GDG Meeting (25/07/12)	VDN declared a non-personal pecuniary interest. VDN attended a meeting in St Petersburg, for which travel and accommodation was funded by Pfizer. The consultancy fee was paid into the NCGC account. Pfizer does not manufacture any IPF related drugs. No other NCGC member had any interests to declare	None
Tenth GDG Meeting (07/09/12)	No interests to declare.	None
Eleventh GDG Meeting (05/10/12)	VN declared a non-personal non-pecuniary interest. VN is attending the Pirfenidone technology appraisal meeting in Manchester on the 24th October. No financial remuneration is being received for this. No other NCGC member had any interests to declare	None
Twelfth GDG Meeting (01/11/12)	No interests to declare.	None
Thirteenth GDG Meeting (06/03/13)	No new interests to declare.	None

Appendix C: Review protocols

Diagnosis

Table 1: Review protocols: biopsy

Review question	In suspected IPF what is the value of **adding biopsy (bronchoscopic biopsy/transbronchial biopsy or surgical lung biopsy)** and /or **bronchoalveolar lavage,** to clinical evaluation, PFTs and CT for confirming the diagnosis of IPF?
Objectives	To determine the added benefit of a biopsy in the diagnosis of a patient with suspected IPF, when clinical history, PFTs, HRCT +/- bronchoalveolar lavage have all be conducted.
Criteria	Population: Adults with suspected ILD Interventions: Baseline clinical assessment (history, PFTs, HRCT, +/- BAL), and: o +/-Bronchoalveolar lavage o Bronchoscopic biopsy/ transbronchial biopsy o Surgical biopsy (open lung or video assisted biopsy) Comparisons: Baseline clinical assessment (history, PFTs, HRCT, +/- BAL) Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • All cause and IPF related mortality • 1 and 3 year survival rates • Sensitivity • Specificity <u>Other outcomes</u> • Adverse events • Improvement in health-related quality of life Population size and directness: No limitations on sample size Populations of people with IPF receiving pharmacological treatment will be included Studies with indirect populations will not be considered Setting: Secondary and tertiary care settings Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search	Databases: Medline, Embase, the Cochrane Library Date: Post 1994 data Language: Restrict to English only Population: ILDs Study designs: Cohort studies
Review	Appraisal of methodological quality: The methodological quality of each study will be assessed

strategy	using NICE checklists. Subgroups: People with co-existent emphysema Type of analysis: Multivariable survival analysis

Table 2: Review protocols: MDT diagnostic consensus

Review question	In suspected IPF what is the additional value of adding multidisciplinary team (MDT) consensus to clinical assessment, PFTs and HRCT in the diagnosis of IPF?
Objectives	To determine whether MDT consensus provides an additional benefit to diagnosis of IPF patients
Criteria	Population: Adults with suspected ILD Interventions: • MDT 1: Clinical assessment + radiological assessment + MDT consensus • MDT 2: Clinical assessment + radiological assessment +/- bronchoaveolar lavage + MDT consensus • MDT 3: Clinical assessment + radiological assessment +/- bronchoaveolar lavage + bronchoscopic/ transbronchical biopsy surgical biopsy (open-lung or VATs) + MDT Comparisons: The following procedures alone or in combination: • Clinical assessment • Radiological assessment • Bronchioalveolar lavage • Bronchscopic/ transbronchial biopsy • Surgical lung biopsy (open lung and video assisted biopsy) Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • All cause and IPF related mortality • 1 and 3 year survival rates • Sensitivity • Specificity <u>Other outcomes</u> • Adverse events • Improvement in health-related quality of life Population size and directness: • No limitations on sample size • Populations of people with IPF receiving pharmacological treatment will be included • Studies with indirect populations will not be considered Setting: Secondary and tertiary care settings Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search	Databases: Medline, Embase, the Cochrane Library Date: Post 1994 data Language: Restrict to English only Population: ILDs Study designs: Cohort studies

Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists. Subgroups: People with co-existent emphysema Type of analysis: Multivariable survival analysis

Table 3: Review protocols: MDT diagnostic composition

Review question	How and by whom is a MDT diagnostic consensus best achieved (i.e. constituency of the MDT, specialist clinics, networks)?
Objectives	To determine what requirements an MDT should fulfil in order to provide optimal clinical care to people with IPF.
Criteria	Population: Adults with suspected ILD Interventions: MDT consisting of RP + R + P in tertiary referral hub as part of wider network Comparisons: Health professionals (RP or R or P) in isolation Health professionals (+/- RP +/-R +/- P) in MDT secondary care tertiary care network of referral between secondary hospitals network of referral between secondary and tertiary hospitals Abbreviations: RP = Respiratory physician (with interest/ experience in ILD) R = Radiologist (with interest/ experience in ILD) P = Pathologist (with interest/ experience in ILD) Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • All cause and IPF related mortality • 1 and 3 year survival rates • Sensitivity • Specificity <u>Other outcomes</u> • Adverse events • Improvement in health-related quality of life Pulation size and directness: No limitations on sample size Populations of people with IPF receiving pharmacological treatment will be included Studies with indirect populations will not be considered Setting: Secondary and tertiary care settings Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search	Databases: Medline, Embase, the Cochrane Library Date: Post 1994 data

	Language: Restrict to English only Population: ILDs Study designs: Cohort studies
Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists. Subgroups: People with co-existent emphysema Type of analysis: Multivariable survival analysis

Prognosis

Table 4: Review protocol: PFTs

Review question	**Do serial pulmonary function tests (resting spirometric, gas transfer measurement and oxygen saturation) predict prognosis of IPF?**
Objectives	To determine whether resting spirometric, gas transfer measurements and oxygen saturation predict prognosis of IPF.
Criteria	Population: Adults with IPF Prognostic Factors: FVC <5% change> TLCO or DLCO <15% change> Oxygen saturation <92%> (Risk factors - Age, sex, smoking status, baseline lung function, previous hospitalisations) Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • Mortality or survival (time to event) <u>Other outcomes</u> • Progression free survival • Acute exacerbation (time to event) • Respiratory hospitalisations (Surrogate outcome for acute exacerbation) • Eligibility for lung transplant We will also indicate if the following are reported in the study (but will not extract actual results for these) • Resource Use –down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness Population size and directness: No limitations on sample size Populations of people with IPF receiving pharmacological treatment will be included Studies with indirect populations will not be considered Setting: Secondary and tertiary care settings Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter

Search	Databases: Medline, Embase, the Cochrane Library, CINAHL Date: Post 1994 data Language: Restrict to English only Population: IPF only Study designs: Cohorts
Review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists. Subgroups: People with co-existent emphysema Type of analysis: Multivariable survival analysis

Table 5: Review protocol: Sub-maximal exercise testing

Review question	**Does baseline sub-maximal exercise testing predict prognosis of IPF?**
Objectives	To determine whether baseline sub-maximal exercise testing predicts prognosis of IPF.
Criteria	Population: Adults with IPF Prognostic factor: Sub-maximal exercise testing (threshold unknown – query <250m>) (Risk factors - Age, sex, smoking status, baseline lung function) Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • Mortality or survival (time to event) <u>Other outcomes</u> • Progression free survival • Acute exacerbation (time to event) • Respiratory hospitalisations (Surrogate outcome for acute exacerbation) • Eligibility for lung transplant We will also indicate if the following are reported in the study (but will not extract actual results for these) • Resource Use –down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness Population size and directness: No limitations on sample size Populations of people with IPF receiving pharmacological treatment will be included Studies with indirect populations will not be considered Setting: Secondary and tertiary care settings Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search Strategy	Databases: Medline, Embase, the Cochrane Library, CINAHL Date: Post 1994 data

	Language: Restrict to English only Population: IPF only Study designs: Cohort studies
Review Strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists. Subgroups: People with co-existent emphysema Type of analysis: Multivariable survival analysis

Table 6: Review protocol: echocardiography

Review question	**Does baseline echocardiography predict prognosis of IPF?**
Objectives	Does baseline echocardiography predict prognosis of IPF?
Criteria	Population: Adults with IPF Prognostic factor: Pulmonary arterial systolic pressure (threshold unknown) (Risk factors - Age, sex, smoking status, baseline lung function) Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • Mortality or survival (time to event) <u>Other outcomes</u> • Progression free survival • Acute exacerbation (time to event) • Respiratory hospitalisations (Surrogate outcome for acute exacerbation) • Eligibility for lung transplant We will also indicate if the following are reported in the study (but will not extract actual results for these) • Resource Use –down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness Population size and directness: • No limitations on sample size • Populations of people with IPF receiving pharmacological treatment will be included • Studies with indirect populations will not be considered Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search Strategy	Databases: Medline, Embase, the Cochrane Library Date: Post 1994 data Language: Restrict to English only Population: IPF only Study designs: Cohort studies
Review Strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists. Subgroups: People with co-existent emphysema Type of analysis: Multivariable survival analysis

Table 7: Review protocol: CT scores

Review question	Do baseline CT scores predict prognosis of IPF?
Objectives	To determine whether baseline CT scores predicts prognosis of IPF.
Criteria	Population: Adults with IPF Prognostic factor: CT features/patterns (Risk factors - Age, sex, smoking status, baseline lung function) Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • Mortality or survival (time to event) <u>Other outcomes</u> • Progression free survival • Acute exacerbation (time to event) • Respiratory hospitalisations (Surrogate outcome for acute exacerbation) • Eligibility for lung transplant We will also indicate if the following are reported in the study (but will not extract actual results for these) • Resource Use –down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness Population size and directness: • No limitations on sample size • Populations of people with IPF receiving pharmacological treatment will be included • Studies with indirect populations will not be considered Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search Strategy	Databases: Medline, Embase, the Cochrane Library Date: Post 1994 data Language: Restrict to English only Population: IPF only Study designs: Cohort studies
Review Strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists. Subgroups: People with co-existent emphysema Type of analysis: Multivariable survival analysis

Pulmonary rehabilitation

Table 8: Review protocol: pulmonary rehabilitation

Review question	What are the benefits of pulmonary rehabilitation programmes for people with confirmed IPF? What is the optimal course content, setting and duration for people referred for pulmonary rehabilitation programmes?

Objectives	To determine the benefits or harms of pulmonary rehabilitation and the requirements of a pulmonary rehabilitation programme to provide optimal symptomatic relief people with IPF.
Criteria	Population: Adult people with IPF Interventions: Pulmonary rehabilitation Comparisons: • Best usual care/ usual medical management • Self-management Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • All cause and IPF related mortality • 1 and 3 year survival rates <u>Other outcomes</u> • Dyspnoea • Hospitalisations due to IPF complications (including IPF exacerbations) • Improvement in cough and breathlessness • Improvement in health-related quality of life • Performance on sub-maximal walk test (distance walked and lowest SaO2) • Improvement in psychosocial health (including depression) We will also indicate if the following are reported in the study (but will not extract actual results for these) • Resource Use –down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness Population size and directness: • No limitations on sample size • Studies with indirect populations such as people with ILD and restrictive lung disease will be considered Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search	Databases: Medline, Embase, the Cochrane Library, CINAHL, PsychInfo Date: All years Language: Restrict to English only Population: Extended to ILDs Study designs: RCTs, systematic reviews, cohort studies
Review strategy	Quality of life data: Collect all data for the stated QoL measure, for meta-analysis and GRADE report only overall scores Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists and GRADE. Data synthesis of RCT data: Meta-analysis where appropriate will be conducted. Meta-analysis where appropriate will be conducted. Subgroups: People with co-existent emphysema

	Type of analysis: Available case analysis

Best supportive care

Table 9: Review protocol: best supportive care

Review question	What is the clinical and cost effectiveness of best supportive care (palliation of cough, breathlessness and fatigue, and oxygen management) in the symptomatic relief of patients with IPF?
Objectives	To determine the most clinically and cost effective best supportive care for patients with IPF
Criteria	Population: Adults with confirmed IPF/ or ILD Interventions: • Oxygen management • Palliation of cough • Palliation of breathlessness • Palliation of fatigue Comparisons: • No treatment • Other treatments Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcome</u> • Improvement in health-related quality of life <u>Other outcomes</u> • Hospitalisations due to IPF complications (including IPF exacerbations) • Improvement in cough and breathlessness • Improvement in psychosocial health (including depression) • Mortality • Performance on sub-maximal walk test (distance walked and lowest SaO2) • Symptom relief We will also indicate if the following are reported in the study (but will not extract actual results for these) • Resource Use –down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness Population size and directness: • No limitations on sample size • Studies with indirect populations will not be considered Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search	Databases: Medline, Embase, the Cochrane Library, CINAHL, PsychInfo Date: All years Language: Restrict to English only Study designs: RCTs, systematic reviews, cohort studies

Review strategy	Quality of life data: Collect all data for the stated QoL measure, for meta-analysis and GRADE report only overall scores Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists and GRADE. Data synthesis of RCT data: Meta-analysis where appropriate will be conducted. Meta-analysis where appropriate will be conducted. Subgroups: People with co-existent emphysema Type of analysis: Available case analysis

Psychosocial support

Table 10: Review protocol: psychosocial support

Review question	What is the specific type of psychosocial support and information that should be provided for patients diagnosed with IPF?
Objectives	To determine what psychosocial support and information should be provided for patients diagnosed with IPF.
Criteria	Population: Adults with confirmed IPF and/ or ILD Intervention: Psychosocial support, Patient information Comparison: None Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • Improvement in health-related quality of life <u>Other outcomes</u> • Dyspnoea • Improvement in psychosocial health (including depression) We will also indicate if the following are reported in the study (but will not extract actual results for these) • Resource Use –down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness Population size and directness: • No limitations on sample size • Studies with indirect populations will not be considered Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search	Databases: Medline, Embase, the Cochrane Library, CINAHL, PsychInfo Date: All years Language: Restrict to English only Study designs: RCTs, systematic reviews of RCTS, cohort studies
Review strategy	Quality of life data: Collect all data for the stated QoL measure, for meta-analysis and GRADE report only overall scores Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists and GRADE.

	Data synthesis of RCT data: Meta-analysis where appropriate will be conducted. Meta-analysis where appropriate will be conducted. Subgroups: People with co-existent emphysema Type of analysis: Available case analysis

Table 11: Review protocol: pharmacological interventions

Review question	**Which drug should be initiated first, for how long, and what combination in the treatment of IPF?** **What is the clinical and cost effectiveness of pharmacological interventions to manage patients with suspected or confirmed IPF:**
Objectives	To determine which treatment should be initiated first, for how long and what are the benefits or harms of the different pharmacological therapies in treating patients with IPF.
Criteria	Population: Adult patients with IPF Interventions: • prednisolone • mycophenolate mofetil • warfarin • azathioprine • N-acetyl cysteine • proton-pump inhibitors • co-trimoxazole • ambrisentan • bosentan • sildenafil • drug combinations Comparisons: • Other pharmacological treatments/ placebo Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • All cause and IPF related mortality • 1 and 3 year survival rates <u>Other outcomes</u> • Adverse events (please see adverse events table listed in Appendix N) • Dyspnoea • Change in percent predicted DLCO • Hospitalisations due to IPF complications, including IPF exacerbations • Improvement in health-related quality of life • Change in percent predicted forced vital capacity • Performance on sub-maximal walk test (distance walked and lowest SaO2) We will also indicate if the following are reported in the study (but will not extract actual results for these) • Resource Use –down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness

	Population size and directness: • No limitations on sample size • Studies with indirect populations will not be considered Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search	Databases: Medline, Embase, the Cochrane Library Date: All years Language: Restrict to English only Population: IPF only Study designs: RCTs and systematic reviews of RCTs
Review strategy	Quality of life data: Collect all data for the stated QoL measure, for meta-analysis and GRADE report only overall scores Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists and GRADE. Data synthesis of RCT data: Meta-analysis where appropriate will be conducted. Meta-analysis where appropriate will be conducted. Subgroups: People with co-existent emphysema Type of analysis: Available case analysis

Table 12: Review protocol: minimising adverse events

Review question	Which measures can be taken to minimize the occurrence/severity of adverse events when undergoing pharmacological treatment for IPF?
Objectives	To determine the severity of adverse events when undergoing pharmacological treatment for patients with confirmed IPF
Criteria	Population: Adult patients with confirmed IPF consistent with ATS/ERS consensus Interventions: Assessing TPMT Comparisons: Not assessing TPMT Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • All cause and IPF related mortality • 1 and 3 year survival rates <u>Other outcomes</u> • Adverse events (please see adverse events table listed in Appendix N) • Dyspnoea • Hospitalisations due to IPF complications, including IPF exacerbations • Improvement in health-related quality of life • Performance on sub-maximal walk test (distance walked and lowest SaO2) We will also indicate if the following are reported in the study (but will not extract actual results for these)

	• Resource Use –down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness Population size and directness: No limitations on sample size Studies with indirect populations will not be considered Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search	Databases: Medline, Embase, the Cochrane Library, Date: All years Language: Restrict to English only Population: IPF only Study designs: No restrictions on study designs
Review strategy	Quality of life data: Collect all data for the stated QoL measure, for meta-analysis and GRADE report only overall scores Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists and GRADE. Data synthesis of RCT data Meta-analysis where appropriate will be conducted. Meta-analysis where appropriate will be conducted. Subgroups: People with co-existent emphysema Type of analysis: Available case analysis

Lung transplantation

Table 13: Review protocol: Lung transplantation

Review question	**What is the optimal timing to consider a patient with IPF for lung transplantation referral?**
Objectives	To determine when in the IPF care pathway a patient should be considered for lung transplantation referral.
Criteria	Population: Adults with confirmed IPF Interventions: Time of assessment for lung/pulmonary transplantation Comparisons: • Different timings in the IPF care pathway according to the different levels of disease severity • No assessment Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • All cause and IPF related Mortality • 1 and 3 year survival rates <u>Other outcomes</u>

	• Cross-over time • Hospitalisations due to IPF complications (including IPF exacerbations) • Improvement of health-related quality of life • Occurrence lung transplantation We will also indicate if the following are reported in the study (but will not extract actual results for these) • Resource Use –down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness Population size and directness: • No limitations on sample size • Studies with indirect populations will not be considered Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search	Databases: Medline, Embase, the Cochrane Library, Date: All years Language: Restrict to English only Population: IPF only Study designs: RCTs, systematic reviews of RCTs, cohorts
Review strategy	Quality of life data: Collect all data for the stated QoL measure, for meta-analysis and GRADE report only overall scores Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists and GRADE. Data synthesis of RCT data: Meta-analysis where appropriate will be conducted. Meta-analysis where appropriate will be conducted. Type of analysis: Available case analysis

Ventilation

Table 14: Review protocol: ventilation

Review question	In acute or acute-on chronic respiratory failure in patients with IPF, what is the value of non-invasive and invasive ventilation?
Objectives	To determine the benefit of non-invasive and invasive ventilation.
Criteria	Population: Adults with confirmed IPF Interventions: Invasive ventilation Comparisons: • Non-invasive ventilation • No ventilation Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcome</u> • Mortality (in hospital and post discharge)

	Other outcomes • Improvement of health-related quality of life • Hospital length of stay We will also indicate if the following are reported in the study (but will not extract actual results for these) • Resource Use –down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness Population size and directness: • No limitations on sample size • Studies with indirect populations will not be considered Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search	Databases: Medline, Embase, the Cochrane Library, Date: All years Language: Restrict to English only Population: IPF only Study designs: RCTs, systematic reviews of RCTs, cohorts
Review strategy	Quality of life data: Collect all data for the stated QoL measure, for meta-analysis and GRADE report only overall scores Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists and GRADE. Data synthesis of RCT data: Meta-analysis where appropriate will be conducted. Meta-analysis where appropriate will be conducted. Type of analysis: Available case analysis

Review and follow-up

Table 15: Review protocol: review and follow-up

Review question	**a. How often should a patient with confirmed diagnosis of IPF be reviewed?** **b. In which healthcare setting and by whom should a review appointment for patients with confirmed IPF be conducted?**
Objectives	To determine the frequency, healthcare setting and healthcare professionals that should conduct the following at a review appointment: • Clinical history and examination • Oxygen assessment • Sub-maximal exercise testing
Criteria	Population: Adults with confirmed IPF Interventions: • Review at 3 and 6 months • Review earlier than 3 months if clinically indicated • Review at yearly intervals

	Comparisons: • Different timing of review • No review Outcomes at following time intervals: original study definitions will be used and recorded <u>Critical outcomes</u> • Change in percent predicted forced vital capacity • Change in percent predicted DLCO <u>Other outcomes</u> • Oxygen saturation at rest • Oxygen saturation on walking • Distance walked on 6 min walk or incremental shuttle walk test • Eligibility for lung transplant Minimally important differences: Please refer to section 3.3.9 Imprecision in the methodology chapter
Search	Databases: Medline, Embase, the Cochrane Library, Date: All years Language: Restrict to English only Population: IPF only Study designs: No restrictions on study design
Review strategy	Quality of life data: Collect all data for the stated QoL measure, for meta-analysis and GRADE report only overall scores Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists and GRADE. Data synthesis of RCT data: Meta-analysis where appropriate will be conducted. Meta-analysis where appropriate will be conducted. Type of analysis: Available case analysis

Appended economic review protocol

Table 16: Appended economic review protocol

Review question	**All questions – health economic evidence**
Objectives	To identify economic studies relevant to the review questions set out above.
Criteria	Populations, interventions and comparators as specified in the individual review protocols above. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Search strategy	An economic study search was undertaken using population specific terms and an economic study filter – see Appendix D
Review strategy	Each study is assessed using the NICE economic evaluation checklist – NICE (2009) Guidelines Manual. Inclusion/exclusion criteria If a study is rated as both 'Directly applicable' and 'minor limitations' (using the NICE economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile.

	If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. If a study is rated as 'Partially applicable' and/or 'potentially serious limitations' then there is discretion over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline and current NHS setting. Where exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: unpublished reports unless submitted as part of a call for evidence letters editorials reviews of economic evaluations foreign language articles Where there is discretion The health economist should be guided by the following hierarchies. Setting: UK NHS OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden) OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) Non-OECD settings (always 'Not applicable') Economic study type: Cost-utility analysis Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis) Comparative cost analysis Non-comparative cost analyses including cost of illness studies (always 'Not applicable') Year of analysis: The more recent the study, the more applicable it is Quality and relevance of effectiveness data used in the economic analysis: The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.

Appendix D: Literature search strategy

Search strategies used for the idiopathic pulmonary fibrosis guideline are outlined below and were run as per the NICE Guidelines Manual 2009 http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf .

Searches for the **clinical reviews** were run in Medline (Ovid), Embase (Ovid) and the Cochrane Library. Additional searches were run in Cinahl (EBSCO) and PsychInfo (Ovid) for some questions. Usually, searches were constructed in the following way:

- A PICO format was used for **intervention** searches where population (P) terms were combined with intervention (I) and sometimes comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

- A PEO format was used for **prognosis** searches where population (P) terms were combined with exposure (E) terms and sometimes outcomes (O). Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). Searches in NHS EED, HTA and HEED were constructed only using population terms. For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy.

All searches were run up to 1st November 2012 unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text.

The search strategies are presented below in the following order:

Section D.1	Population terms by database. The same searches were used for all questions and for both clinical and health economic searches.
Section D.2	Study filter terms by database. These include filters for epidemiological study designs, health economic studies, quality of life studies and disease progression studies.
Section D.3	Searches run for specific questions with the intervention or exposure terms by database. Order as presented in guideline
Section D.3.1	Diagnosis: biopsy/lavage
Section D.3.2	Diagnosis: MDT
Section D.3.3	Prognosis: PFTs
Section D.3.4	Prognosis: sub maximal exercise testing
Section D.3.5	Prognosis: HRCT/echocardiography
Section D.3.6	Psychosocial support
Section D.3.7	Best supportive care/ patient review and follow up
Section D.3.8	Pulmonary rehabilitation
Section D.3.9	Pharmacological interventions
Section D.3.10	Pharmacological interventions: adverse events
Section D.3.11	Lung transplantation
Section D.3.12	Ventilation
Section D.4	Economics search

D.1 Population search strategies

D.1.1 IPF population terms

Medline search terms

1	Idiopathic Pulmonary Fibrosis/
2	Idiopathic Interstitial Pneumonias/
3	Lung Diseases, Interstitial/
4	((idiopathic adj (pulmonary or interstitial) adj (fibros* or pneumonia*)) or (fibrosing adj alveolitis) or interstitial lung disease* or ((chronic or usual or fibrosing) adj interstitial pneumonia*) or ((lung or pulmonary or idiopathic) adj interstitial fibros*) or (alveolar fibros* adj3 lung*) or (diffuse adj3 (lung or pulmonary) adj fibros*) or ((interstitial or parenchymal or fibrotic or restrictive) adj lung disease*)).ti,ab.
5	or/1-4
6	limit 5 to English language
7	letter/
8	editorial/
9	news/
10	exp historical article/
11	Anecdotes as Topic/
12	comment/
13	case report/
14	(letter or comment*).ti.
15	or/7-14
16	randomized controlled trial/ or random*.ti,ab.
17	15 not 16
18	animals/ not humans/
19	Animals, Laboratory/
20	exp animal experiment/
21	exp animal model/
22	exp Rodentia/
23	(rat or rats or mouse or mice).ti.
24	or/17-23
25	6 not 24

Embase search terms

1	fibrosing alveolitis/
2	interstitial pneumonia/
3	interstitial lung disease/
4	((idiopathic adj (pulmonary or interstitial) adj (fibros* or pneumonia*)) or (fibrosing adj alveolitis) or interstitial lung disease* or ((chronic or usual or fibrosing) adj interstitial pneumonia*) or ((lung or pulmonary or idiopathic) adj interstitial fibros*) or (alveolar fibros* adj3 lung*) or (diffuse adj3 (lung or pulmonary) adj fibros*) or ((interstitial or parenchymal or fibrotic or restrictive) adj lung disease*)).ti,ab.
5	or/1-4
6	limit 5 to English language
7	letter.pt. or letter/

8	note.pt.
9	editorial.pt.
10	case report/ or case study/
11	(letter or comment*).ti.
12	or/7-11
13	randomized controlled trial/ or random*.ti,ab.
14	12 not 13
15	animal/ not human/
16	nonhuman/
17	exp Animal Experiment/
18	exp Experimental Animal/
19	animal model/
20	exp Rodent/
21	(rat or rats or mouse or mice).ti.
22	or/14-21
23	5 not 22

Cinahl search terms

S1	(lung or pulmonary) n1 fibros*
S2	alveolitis n3 extrinsic
S3	lung disease* n3 (restrictive or interstitial)
S4	(MH "Pulmonary Fibrosis")
S5	S1 or S2 or S3 or S4
S6	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S7	S5 NOT S6

Cochrane search terms

#1	MeSH descriptor Idiopathic Pulmonary Fibrosis, this term only
#2	MeSH descriptor Idiopathic Interstitial Pneumonias, this term only
#3	MeSH descriptor Lung Diseases, Interstitial, this term only
#4	((idiopathic NEAR (pulmonary or interstitial) NEAR (fibros* or pneumonia*)) or (fibrosing NEAR alveolitis) or interstitial lung disease* or ((chronic or usual or fibrosing) NEAR interstitial pneumonia*) or ((lung or pulmonary or idiopathic) NEAR interstitial fibros*) or (alveolar fibros* NEAR/3 lung*) or (diffuse NEAR/3 (lung or pulmonary) adj fibros*) or ((interstitial or parenchymal or fibrotic or restrictive) NEAR lung disease*)):ti,ab
#5	(#1 OR #2 OR #3 OR #4)

PsychInfo search terms

1	((idiopathic adj (pulmonary or interstitial) adj (fibros* or pneumonia*)) or (fibrosing adj alveolitis) or interstitial lung disease* or ((chronic or usual or fibrosing) adj interstitial pneumonia*) or ((lung or pulmonary or idiopathic) adj interstitial fibros*) or (alveolar fibros* adj3 lung*) or (diffuse adj3 (lung or pulmonary) adj fibros*) or ((interstitial or parenchymal or fibrotic or restrictive) adj lung disease*)).ti,ab.
2	((lung or pulmonary) adj fibros*).ti,ab.

3	or/1-2
4	limit 3 to English language

D.1.2 ILD population terms

Medline search terms

1	Restrictive lung disease*.ti,ab.
2	Pulmonary fibrosis.ti,ab.
3	((idiopathic adj (pulmonary or interstitial) adj (fibros* or pneumonia*)) or (fibrosing adj alveolitis) or interstitial lung disease* or ((chronic or usual or fibrosing) adj interstitial pneumonia*) or ((lung or pulmonary or idiopathic) adj interstitial fibros*) or (alveolar fibros* adj3 lung*) or (diffuse adj3 (lung or pulmonary) adj fibros*) or ((interstitial or parenchymal or fibrotic) adj lung disease*)).ti,ab.
4	Idiopathic Pulmonary Fibrosis/
5	Idiopathic Interstitial Pneumonias/
6	alveolitis, extrinsic allergic/
7	anti-glomerular basement membrane disease/
8	histiocytosis, langerhans-cell/
9	Idiopathic Interstitial Pneumonias/
10	Pneumoconiosis/
11	Radiation Pneumonitis/
12	Sarcoidosis, Pulmonary/
13	Wegener Granulomatosis/
14	pneumonitis, interstitial/
15	((Lung disease* adj3 interstitial) or (Alveolitis adj3 Extrinsic) or anti Glomerular Basement Membrane Disease* or (Histiocytosis adj3 Langerhans*) or Idiopathic Interstitial Pneumonia* or pneumoconiosis or Radiation Pneumonitis or (Sarcoidosis adj3 Pulmonary) or Wegener Granulomatosis or (pneumoni* adj3 interstitial) or diffuse parenchymal lung disease*).ti,ab.
16	or/1-15
17	limit 16 to English language
18	letter/
19	editorial/
20	news/
21	exp historical article/
22	Anecdotes as Topic/
23	comment/
24	case report/
25	(letter or comment*).ti.
26	or/89-25
27	randomized controlled trial/ or random*.ti,ab.
28	26 not 287
29	animals/ not humans/
30	Animals, Laboratory/
31	exp animal experiment/
32	exp animal model/
33	exp Rodentia/
34	(rat or rats or mouse or mice).ti.

35	or/28-34
36	17 not 35

Embase search terms

1	((idiopathic adj (pulmonary or interstitial) adj (fibros* or pneumonia*)) or (fibrosing adj alveolitis) or interstitial lung disease* or ((chronic or usual or fibrosing) adj interstitial pneumonia*) or ((lung or pulmonary or idiopathic) adj interstitial fibros*) or (alveolar fibros* adj3 lung*) or (diffuse adj3 (lung or pulmonary) adj fibros*) or ((interstitial or parenchymal or fibrotic) adj lung disease*)).ti,ab.
2	fibrosing alveolitis/
3	interstitial pneumonia/
4	((Lung disease* adj3 interstitial) or (Alveolitis adj3 Extrinsic) or anti Glomerular Basement Membrane Disease* or (Histiocytosis adj3 Langerhans*) or Idiopathic Interstitial Pneumonia* or pneumoconiosis or Radiation Pneumonitis or (Sarcoidosis adj3 Pulmonary) or Wegener Granulomatosis or (pneumoni* adj3 interstitial) or diffuse parenchymal lung disease*).ti,ab.
5	lung alveolitis/
6	histiocytosis/
7	pneumoconiosis/
8	radiation pneumonia/
9	lung sarcoidosis/
10	Wegener granulomatosis/
11	Restrictive lung disease*.ti,ab.
12	Pulmonary fibrosis.ti,ab.
13	or/1-12
14	limit 13 to English language
15	letter.pt. or letter/
16	note.pt.
17	editorial.pt.
18	case report/ or case study/
19	(letter or comment*).ti.
20	or/15-19
21	randomized controlled trial/ or random*.ti,ab.
22	20 not 21
23	animal/ not human/
24	nonhuman/
25	exp Animal Experiment/
26	exp Experimental Animal/
27	animal model/
28	exp Rodent/
29	(rat or rats or mouse or mice).ti.
30	or/22-29
31	15 not 31

Cinahl search terms

S1	(lung or pulmonary) n1 fibros*
S2	Alveoliti* n2 fibrosing OR Alveoliti* n2 Extrinsic OR Wegener Granulomatosis OR Histiocytosis n3 Langerhans* OR anti Glomerular Basement Membrane Disease* OR pneumoconiosis OR Radiation Pneumonitis OR Sarcoidosis n3 Pulmonary OR alveolar fibros* n3 lung* OR

	interstitial pneumonia*
S3	lung disease* n3 (restrictive or interstitial)
S4	(MH "Pulmonary Fibrosis") OR (MH "Lung Diseases, Interstitial+")
S5	S1 or S2 or S3 or S4
S6	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT "questions and answers" or PT response or PT software or PT teaching materials or PT website
S7	S5 NOT S6

Cochrane search terms

#1	(idiopathic NEXT (pulmonary or interstitial) NEXT (fibros* or pneumonia*)) or (fibrosing NEXT alveolitis) or (interstitial NEXT lung NEXT disease*) or ((chronic or usual or fibrosing) NEXT interstitial NEXT pneumonia*) or ((lung or pulmonary or idiopathic) NEXT (interstitial NEXT fibros*)) or (alveolar NEXT fibrosis NEAR/3 lung*) or (diffuse NEAR/3 (lung or pulmonary) NEXT fibros*) or ((interstitial or parenchymal or fibrotic) NEXT (lung NEXT disease*)):ti,ab
#2	Restrictive lung disease*:ti,ab
#3	Pulmonary fibrosis:ti,ab
#4	(Lung disease* NEAR/3 interstitial):ti,ab
#5	(Alveolitis NEAR/3 Extrinsic):ti,ab
#6	(Histiocytosis NEAR/3 Langerhans):ti,ab
#7	(Idiopathic Interstitial Pneumonia*):ti,ab
#8	Pneumoconiosis:ti,ab
#9	(Sarcoidosis NEAR/3 Pulmonary):ti,ab
#10	(Wegener NEXT Granulomatosis):ti,ab
#11	(pneumoni* NEAR/3 interstitial):ti,ab
#12	MeSH descriptor Lung Diseases, Interstitial explode all trees
#13	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)

PsychInfo search terms

1	Restrictive lung disease*.ti,ab.
2	Pulmonary fibrosis.ti,ab.
3	((idiopathic adj (pulmonary or interstitial) adj (fibros* or pneumonia*)) or (fibrosing adj alveolitis) or interstitial lung disease* or ((chronic or usual or fibrosing) adj interstitial pneumonia*) or ((lung or pulmonary or idiopathic) adj interstitial fibros*) or (alveolar fibros* adj3 lung*) or (diffuse adj3 (lung or pulmonary) adj fibros*) or ((interstitial or parenchymal or fibrotic) adj lung disease*)).ti,ab.
4	((Lung disease* adj3 interstitial) or (Alveolitis adj3 Extrinsic) or anti Glomerular Basement Membrane Disease* or (Histiocytosis adj3 Langerhans*) or Idiopathic Interstitial Pneumonia* or pneumoconiosis or Radiation Pneumonitis or (Sarcoidosis adj3 Pulmonary) or Wegener Granulomatosis or (pneumoni* adj3 interstitial) or diffuse parenchymal lung disease*).ti,ab.
5	or/1-4
6	limit 5 to English language

D.2 Study filter search terms

D.2.1 Systematic review search terms

Medline search terms

1	Meta-Analysis/
2	Meta-Analysis as Topic/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	((indirect or mixed) adj2 comparison*).ti,ab.
11	or/1-10

Embase search terms

1	systematic review/
2	meta-analysis/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	((indirect or mixed) adj2 comparison*).ti,ab.
12	or/1-11

D.2.2 Randomised controlled studies (RCTs) search terms

Medline search terms

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomi#ed.ab.
4	placebo.ab.
5	randomly.ab.
6	Clinical Trials as topic.sh.
7	trial.ti.
8	or/1-7

Embase search terms

1	random*.ti,ab.
2	factorial*.ti,ab.
3	(crossover* or cross over*).ti,ab.
4	((doubl* or singl*) adj blind*).ti,ab.
5	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6	crossover procedure/
7	single blind procedure/
8	randomized controlled trial/
9	double blind procedure/
10	or/1-9

D.2.3 Diagnostic accuracy search terms

Medline search terms

1	exp "sensitivity and specificity"/
2	(sensitivity or specificity).ti,ab.
3	((pre test or pretest or post test) adj probability).ti,ab.
4	(predictive value* or PPV or NPV).ti,ab.
5	likelihood ratio*.ti,ab.
6	likelihood function/
7	(ROC curve* or AUC).ti,ab.
8	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9	gold standard.ab.
10	or/1-9

Embase search terms

1	exp "sensitivity and specificity"/
2	(sensitivity or specificity).ti,ab.
3	((pre test or pretest or post test) adj probability).ti,ab.
4	(predictive value* or PPV or NPV).ti,ab.
5	likelihood ratio*.ti,ab.
6	(ROC curve* or AUC).ti,ab.
7	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
8	diagnostic accuracy/
9	diagnostic test accuracy study/
10	gold standard.ab.
11	or/1-10

D.2.4 Observational studies search terms

Medline search terms

1	Epidemiologic studies/
2	exp Case control studies/
3	exp Cohort studies/
4	Cross-sectional studies/

5	case control.ti,ab.
6	(cohort adj (study or studies or analys*)).ti,ab.
7	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9	or/1-8

Embase search terms

1	Clinical study/
2	exp Case control study/
3	Family study/
4	Longitudinal study/
5	Retrospective study/
6	Prospective study/
7	Cross-sectional study/
8	Cohort analysis/
9	Follow-up/
10	cohort*.ti,ab.
11	9 and 10
12	case control.ti,ab.
13	(cohort adj (study or studies or analys*)).ti,ab.
14	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16	or/1-8,11-15

D.2.5 Prognosis search terms

Medline search terms

1	Prognosis/
2	Predictive value of tests/
3	(predict* or prognos* or progression).ti,ab.
4	or/1-3

Embase search terms

1	*prognosis/
2	*predictive value/
3	*disease exacerbation/
4	(predict* or prognos* or progression).ti,ab.
5	or/1-4

D.2.6 Health economic search terms

Medline search terms

1	Economics/
2	Value of life/

3	exp "Costs and Cost Analysis"/
4	exp Economics, Hospital/
5	exp Economics, Medical/
6	Economics, Nursing/
7	Economics, Pharmaceutical/
8	exp "Fees and Charges"/
9	exp Budgets/
10	budget*.ti,ab.
11	cost*.ti.
12	(economic* or pharmaco?economic*).ti.
13	(price* or pricing*).ti,ab.
14	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15	(financ* or fee or fees).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	or/1-16

Embase search terms

1	health economics/
2	exp economic evaluation/
3	exp health care cost/
4	exp fee/
5	budget/
6	funding/
7	budget*.ti,ab.
8	cost*.ti.
9	(economic* or pharmaco?economic*).ti.
10	(price* or pricing*).ti,ab.
11	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12	(financ* or fee or fees).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	or/1-13

D.2.7 Quality of life search terms

Medline search terms

1	quality-adjusted life years/
2	sickness impact profile/
3	(quality adj2 (wellbeing or well being)).ti,ab.
4	sickness impact profile.ti,ab.
5	disability adjusted life.ti,ab.
6	(qal* or qtime* or qwb* or daly*).ti,ab.
7	(euroQoL* or eq5d* or eq 5*).ti,ab.
8	(QoL* or hql* or hQoL* or h QoL* or hrQoL* or hr QoL*).ti,ab.
9	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
10	(hui or hui1 or hui2 or hui3).ti,ab.
11	(health* year* equivalent* or hye or hyes).ti,ab.

12	discrete choice*.ti,ab.
13	rosser.ti,ab.
14	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
16	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
18	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
19	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
20	or/1-19

Embase search terms

1	quality adjusted life year/
2	"quality of life index"/
3	short form 12/ or short form 20/ or short form 36/ or short form 8/
4	sickness impact profile/
5	(quality adj2 (wellbeing or well being)).ti,ab.
6	sickness impact profile.ti,ab.
7	disability adjusted life.ti,ab.
8	(qal* or qtime* or qwb* or daly*).ti,ab.
9	(euroQoL* or eq5d* or eq 5*).ti,ab.
10	(QoL* or hql* or hQoL* or h QoL* or hrQoL* or hr QoL*).ti,ab.
11	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
12	(hui or hui1 or hui2 or hui3).ti,ab.
13	(health* year* equivalent* or hye or hyes).ti,ab.
14	discrete choice*.ti,ab.
15	rosser.ti,ab.
16	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
18	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
20	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
21	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
22	or/1-21

D.2.8 Economic modelling search terms

Medline search terms

1	exp models, economic/
2	*Models, Theoretical/
3	*Models, Organizational/
4	markov chains/
5	monte carlo method/
6	exp Decision Theory/
7	(markov* or monte carlo).ti,ab.
8	econom* model*.ti,ab.
9	(decision* adj2 (tree* or analy* or model*)).ti,ab.

10	or/1-9

Embase search terms

1	statistical model/
2	exp economic aspect/
3	1 and 2
4	*theoretical model/
5	*nonbiological model/
6	stochastic model/
7	decision theory/
8	decision tree/
9	monte carlo method/
10	(markov* or monte carlo).ti,ab.
11	econom* model*.ti,ab.
12	(decision* adj2 (tree* or analy* or model*)).ti,ab.
13	or/3-12

D.2.9 Disease progression search terms

Medline search terms

1	exp disease progression/
2	exp "Severity of Illness Index"/
3	"International Classification of Diseases"/
4	(Disease* adj (classif* or progress* or course*)).ti,ab.
5	clinical course.ti,ab.
6	(disease adj (attribute* or development* or evolution*)).ti,ab.
7	Natural History/
8	(progress* adj2 (slow* or stable or rapid or fast or quick*)).ti,ab.
9	natural history.ti,ab.
10	(predict* adj3 (mortality or death)).ti,ab.
11	(acute adj (worse* or exacerbat*)).ti,ab.
12	or/1-11

Embase search terms

1	*disease classification/
2	*disease course/
3	*disease severity/
4	*disease association/
5	*disease exacerbation/
6	"international classification of diseases"/
7	(Disease* adj (classif* or progress* or course*)).ti,ab.
8	clinical course.ti,ab.
9	(disease adj (attribute* or development* or evolution*)).ti,ab.
10	(progress* adj2 (slow* or stable or rapid or fast or quick*)).ti,ab.
11	natural history.ti,ab.
12	(predict* adj3 (mortality or death)).ti,ab.

13	(acute adj (worse* or exacerbat*)).ti,ab.
14	or/1-13

D.3 Searches by specific questions

D.3.1 Diagnosis: biopsy/bronchoalveolar lavage

In suspected IPF what is the additional value of adding biopsy to clinical evaluation, PFTs, HRCT +/- bronchoalveolar lavage for confirming the diagnosis of IPF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
IPF	Biopsy or lavage		SRs, RCTs, observational, diagnostic (Medline and Embase only)	No date restriction. Search run up to 01/11/12

Biopsy/lavage search terms

Medline search terms

1	exp Biopsy/
2	biops*.ti,ab.
3	exp Bronchoalveolar Lavage/
4	((bronchoalveolar or alveolar or lung or bronchial or bronchopulmonary) adj2 lavage*).ti,ab.
5	or/1-4

Embase search terms

1	biops*.ti,ab.
2	exp biopsy/ or exp biopsy device/ or exp biopsy technique/
3	lung lavage/
4	((bronchoalveolar or alveolar or lung or bronchial or bronchopulmonary) adj2 lavage*).ti,ab.
5	or/1-4

Cochrane search terms

#1	biops*:ti,ab
#2	MeSH descriptor Biopsy explode all trees
#3	MeSH descriptor Bronchoalveolar Lavage explode all trees
#4	((bronchoalveolar or alveolar or lung or bronchial or bronchopulmonary) NEAR/2 lavage*):ti,ab,kw
#5	(#1 OR #2 OR #3 OR #4)

D.3.2 Diagnosis: MDT

Searches for the following two questions were run as one search:

In suspected IPF what is the additional value of adding multidisciplinary team (MDT) consensus to clinical assessment, PFTs and HRCT in the diagnosis of IPF?

How and by whom is an MDT diagnostic consensus best achieved (i.e. constituency of the MDT, specialist clinics, networks)?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
ILD	MDT		None, all study types considered	No date restriction. Search run up to 01/11/12

MDT search terms

Medline search terms

1	((doctor* or physician* or pulmonologist* or specialist* or clinician*) and radiologist*).ti,ab.
2	(Radiol* and (pathol* or histopathol* or histol*)).ti,ab.
3	(Multidisciplinar* or Interdisciplinar* or mdt or mdd or interobserver*).ti,ab.
4	((clinical or diagnos*) adj2 (consensus or agreement*)).ti,ab.
5	((Secondary or tertiary) adj care).ti,ab.
6	(Specialist* adj2 (clinic* or centre* or center* or hub or network*)).ti,ab.
7	(respiratory adj2 (clinic or clinics or hub*)).ti,ab.
8	(chest* adj2 (clinic or clinics or centre* or center* or hub or network*)).ti,ab.
9	(lung* adj2 (clinic or clinics or centre* or center* or hub*)).ti,ab.
10	(clinical adj2 (centre* or center* or hub or network*)).ti,ab.
11	(community adj2 (clinic or clinics or centre* or center* or hub or network*)).ti,ab.
12	exp *"Referral and Consultation"/
13	*Patient Care Team/
14	exp *"Delivery of Health Care"/
15	*Decision Trees/
16	*Physician's Practice Patterns/
17	*observer variation/
18	*Community Medicine/
19	or/1-18

Embase search terms

1	((doctor* or physician* or pulmonologist* or specialist* or clinician*) and radiologist*).ti,ab.
2	(Radiol* and (pathol* or histopathol* or histol*)).ti,ab.
3	(Multidisciplinar* or Interdisciplinar* or mdt or mdd or interobserver*).ti,ab.
4	((clinical or diagnos*) adj2 (consensus or agreement*)).ti,ab.
5	((Secondary or tertiary) adj care).ti,ab.
6	(Specialist* adj2 (clinic* or centre* or center* or hub or network*)).ti,ab.
7	(respiratory adj2 (clinic or clinics or hub*)).ti,ab.
8	(chest* adj2 (clinic or clinics or centre* or center* or hub or network*)).ti,ab.
9	(lung* adj2 (clinic or clinics or centre* or center* or hub*)).ti,ab.
10	(clinical adj2 (centre* or center* or hub or network*)).ti,ab.
11	(community adj2 (clinic or clinics or centre* or center* or hub or network*)).ti,ab.
12	exp *patient care/
13	exp *health care delivery/

14	*"decision tree"/
15	*consensus/
16	*observer variation/
17	*community medicine/
18	*intermethod comparison/
19	*medical practice/
20	*differential diagnosis/
21	*quantitative diagnosis/
22	*diagnostic accuracy/
23	*"medical record review"/
24	*patient referral/
25	or/1-24

Cinahl search terms

S1	Multidisciplinar* OR Interdisciplinar* OR mdt OR mdd OR interobserv*
S2	clinical n2 consensus OR clinical n2 agreement* OR diagnos* n2 consensus OR diagnos* n2 agreement*
S3	doctor* OR physician* OR pulmonologist* OR specialist* OR clinician*
S4	radiologist*
S5	S3 and S4
S6	pathol* OR histopathol* OR histol*
S7	Radiol*
S8	S6 and S7
S9	Secondary care OR tertiary care OR Specialist* n2 clinic* OR Specialist* n2 centre* OR Specialist* n2 center* OR Specialist* n2 hub OR Specialist* n2 network* OR respiratory n2 clinic OR respiratory n2 clinics OR respiratory n2 hub*
S10	chest* n2 clinic OR chest* n2 clinics OR chest* n2 centre* OR chest* n2 center* OR chest* n2 hub* OR chest* n2 network* OR lung* n2 clinic OR lung* n2 clinics OR lung* n2 centre* OR lung* n2 center* OR lung* n2 hub* OR lung* n2 network*
S11	community n2 clinic OR community n2 clinics OR community n2 centre* OR community n2 center* OR community n2 hub* OR community n2 network* OR clinical n2 centre* OR clinical n2 center* OR clinical n2 hub* OR clinical n2 network*
S12	(MH "Referral and Consultation+")
S13	(MH "Multidisciplinary Care Team")
S14	(MM "Health Care Delivery+")
S15	(MM "Decision Support Techniques+")
S16	(MM "Practice Patterns")
S17	S1 or S2 or S5 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16

Cochrane search terms

#1	((doctor* or physician* or pulmonologist* or specialist* or clinician*) and radiologist*):ti,ab
#2	(Radiol* and (pathol* or histopathol* or histol*)):ti,ab
#3	(Multidisciplinar* or Interdisciplinar* or mdt or mdd or interobserver*):ti,ab
#4	((clinical or diagnos*) NEAR/2 (consensus or agreement*)):ti,ab
#5	((Secondary or tertiary) NEXT care):ti,ab
#6	(Specialist* NEAR/2 (clinic* or centre* or center* or hub or network*)):ti,ab
#7	(respiratory NEAR/2 (clinic or clinics or hub*)):ti,ab

#8	(chest* NEAR/2 (clinic or clinics or centre* or center* or hub or network*)):ti,ab
#9	(lung* NEAR/2 (clinic or clinics or centre* or center* or hub*)):ti,ab
#10	(clinical NEAR/2 (centre* or center* or hub or network*)):ti,ab
#11	(community NEAR/2 (clinic or clinics or centre* or center* or hub or network*)):ti,ab
#12	MeSH descriptor Referral and Consultation explode all trees
#13	MeSH descriptor Patient Care Team, this term only
#14	MeSH descriptor Delivery of Health Care explode all trees
#15	MeSH descriptor Decision Trees, this term only
#16	MeSH descriptor Physician's Practice Patterns, this term only
#17	MeSH descriptor Observer Variation, this term only
#18	MeSH descriptor Community Medicine, this term only
#19	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)

D.3.3 Prognosis: PFTs

Do serial pulmonary function tests (resting spirometric, gas transfer measurement and oxygen saturation) predict prognosis of IPF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
IPF	Pulmonary function tests (PFTs)		Observational studies, prognostic studies (Medline and Embase only)	1994- 01/11/12

PFT search terms

Medline search terms

1	(forced adj vital adj capacity*).ti,ab.
2	Fvc.ti,ab.
3	(forced adj expiratory adj volume*).ti,ab.
4	Fev*1.ti,ab.
5	(diffusing adj capacity adj3 (carbon adj monoxide)).ti,ab.
6	Dlco.ti,ab.
7	Tlco.ti,ab.
8	Tlc.ti,ab.
9	(total adj lung adj capacity*).ti,ab.
10	(lung adj volume*).ti,ab.
11	((pulmonary or lung) adj (function adj test*)).ti,ab.
12	(oxygen adj saturat*).ti,ab.
13	oximetry.ti,ab.
14	Spiromet*.ti,ab.
15	Vital capacity/
16	Forced expiratory volume/

17	Pulmonary gas exchange/
18	Pulmonary diffusing capacity/
19	Lung volume measurements/
20	Respiratory function tests/
21	*oxygen consumption/
22	Oximetry/
23	*oxygen/
24	Spirometry/
25	or/1-24

Embase search terms

1	(forced adj vital adj capacity*).ti,ab.
2	Fvc.ti,ab.
3	(forced adj expiratory adj volume*).ti,ab.
4	Fev*1.ti,ab.
5	(diffusing adj capacity adj3 (carbon adj monoxide)).ti,ab.
6	Dlco.ti,ab.
7	Tlco.ti,ab.
8	Tlc.ti,ab.
9	(total adj lung adj capacity*).ti,ab.
10	(lung adj volume*).ti,ab.
11	(oxygen adj saturat*).ti,ab.
12	((pulmonary or lung) adj (function adj test*)).ti,ab.
13	Spiromet*.ti,ab.
14	Forced vital capacity/
15	Forced expiratory volume/
16	Lung gas exchange/
17	Lung diffusion capacity/
18	Total lung capacity/
19	Lung volume/
20	lung function test/
21	Arterial oxygen tension/
22	Lung alveolus oxygen tension/
23	*oxygen/
24	Oxygen saturation/
25	Spirometry/
26	or/1-25

Cinahl search terms

S1	Forced vital capacity
S2	Fvc
S3	forced expiratory volume*
S4	fev
S5	diffusing n2 capacity
S6	Dlco OR Tlco
S7	Tlc

S8	total lung capacit*
S9	lung volume*
S10	((pulmonary or lung) n2 (function test*))
S11	oxygen saturat*
S12	Oximetry
S13	Spiromet*
S14	MH Vital capacity
S15	MH Pulmonary gas exchange
S16	MH Lung volume measurements
S17	MH Pulmonary diffusing capacity
S18	MH Respiratory function tests
S19	MH oxygen consumption
S20	MH Oximetry
S21	MH oxygen
S22	MH Spirometry
S23	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22

Cochrane search terms

#1	Fvc:ti,ab
#2	(forced NEXT expiratory NEXT volume*):ti,ab
#3	Fev*:ti,ab
#4	((diffusing NEXT capacity) NEAR/3 (carbon NEXT monoxide)):ti,ab
#5	Dlco:ti,ab
#6	Tlco:ti,ab
#7	Tlc:ti,ab
#8	(forced NEXT vital NEXT capacit*):ti,ab
#9	(total NEXT lung NEXT capacit*):ti,ab
#10	(lung NEAR/2 volume*):ti,ab
#11	(oxygen NEAR/2 saturat*):ti,ab
#12	oximtery:ti,ab
#13	Spiromet*:ti,ab
#14	MeSH descriptor Vital Capacity explode all trees
#15	MeSH descriptor Forced Expiratory Volume explode all trees
#16	MeSH descriptor Pulmonary Gas Exchange explode trees 1 and 3
#17	MeSH descriptor Pulmonary Diffusing Capacity explode all trees
#18	MeSH descriptor Lung Volume Measurements explode all trees
#19	MeSH descriptor Oxygen Consumption explode all trees
#20	MeSH descriptor Oximetry explode all trees
#21	MeSH descriptor Oxygen explode tree 2
#22	MeSH descriptor Spirometry explode all trees
#23	((pulmonary or lung) NEAR/2 (function NEXT test*)):ti,ab
#24	MeSH descriptor Respiratory Function Tests explode all trees
#25	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)

D.3.4 Prognosis: sub maximal exercise testing

Does baseline sub-maximal exercise testing predict prognosis of IPF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
IPF	Sub maximal exercise testing		Observational studies, prognostic studies (Medline and Embase only)	1994-01/11/12

Sub maximal exercise testing search terms

Medline search terms

1	("Sub maximal" adj exercis*).ti,ab.
2	(Submaximal adj exercis*).ti,ab.
3	(walk* adj test*).ti,ab.
4	(walk adj distance).ti,ab.
5	(exercise adj test*).ti,ab.
6	(walk adj2 exercis*).ti,ab.
7	(fitness adj test*).ti,ab.
8	(shuttle adj test*).ti,ab.
9	(minute adj walk).ti,ab.
10	6mwt.ti,ab.
11	6mwd.ti,ab.
12	12MWT.ti,ab.
13	exp Exercise Therapy/
14	Exercise Tolerance/
15	Exercise Test/
16	or/1-15

Embase search terms

1	("Sub maximal" adj exercis*).ti,ab.
2	(Submaximal adj exercis*).ti,ab.
3	(walk* adj test*).ti,ab.
4	(walk adj distance).ti,ab.
5	(exercise adj test*).ti,ab.
6	(walk adj2 exercis*).ti,ab.
7	(fitness adj test*).ti,ab.
8	(shuttle adj test*).ti,ab.
9	(minute adj walk).ti,ab.
10	6mwt.ti,ab.
11	6mwd.ti,ab.
12	12MWT.ti,ab.
13	exercise/
14	exercise test/
15	exercise tolerance/

16	cardiopulmonary exercise test/
17	or/1-16

Cinahl search terms

S1	Sub maximal exercis* OR Submaximal exercis*
S2	walk* n1 (test* or distance or exercise* or minute*)
S3	(exercise or fitness or shuttle) n1 test*
S4	6mwt OR 6mwd OR 12MWT
S5	(MH "Therapeutic Exercise") OR (MH "Exercise Therapy: Ambulation (Iowa NIC)") OR (MH "Exercise Tolerance+") OR (MH "Walking") OR (MH "Exercise Test+")
S6	S1 or S2 or S3 or S4 or S5

Cochrane search terms

#1	((Sub NEXT maximal) NEXT exercis*):ti,ab
#2	(walk* NEXT test*):ti,ab
#3	(walk NEXT distance):ti,ab
#4	(walk NEXT exercis*):ti,ab
#5	(exercise NEXT test*):ti,ab
#6	(fitness NEXT test*):ti,ab
#7	(shuttle NEXT test*):ti,ab
#8	(minute NEXT walk):ti,ab
#9	6mwt:ti,ab
#10	6mwd:ti,ab
#11	12MWT:ti,ab
#12	MeSH descriptor Exercise Test explode trees 2 and 3
#13	MeSH descriptor Exercise Therapy explode all trees
#14	MeSH descriptor Exercise Tolerance explode all trees
#15	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)

D.3.5 Prognosis: HRCT/echocardiography

Searches for the following two questions were run as one search:

Does baseline echocardiography predict prognosis of IPF?

Do baseline HRCT scores predict prognosis of IPF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
IPF	HRCT/ echocardiography		Observational studies, prognostic studies (Medline and Embase only)	1994-01/11/12

HRCT/ echocardiography search terms

Medline search terms

1	Hypertension, Pulmonary/di, ri, us [Diagnosis, Radionuclide Imaging, Ultrasonography]

2	*Hypertension, Pulmonary/
3	exp Echocardiography/
4	(echocardio* or tissue Doppler imag* or ((pulmonary or lung*) adj arter* adj2 pressure)).ti,ab.
5	exp Tomography, X-Ray Computed/
6	Lung/ra [Radiography]
7	Lung Diseases/ra [Radiography]
8	lung diseases, interstitial/ra [Radiography]
9	(hrct or (comput* adj3 tomograph*) or ((cat or ct) adj scan*)).ti,ab.
10	or/1-9

Embase search terms

1	*pulmonary hypertension/
2	pulmonary hypertension/di [Diagnosis]
3	exp echocardiography/
4	(echocardio* or tissue Doppler imag* or ((pulmonary or lung*) adj arter* adj2 pressure)).ti,ab.
5	exp computer assisted tomography/
6	(hrct or (comput* adj3 tomograph*) or ((cat or ct) adj scan*)).ti,ab.
7	or/1-6

Cinahl search terms

S1	(MM "Hypertension, Pulmonary") OR (MM "Pulmonary Arterial Hypertension")
S2	(MH "Echocardiography+")
S3	echocardio* OR tissue Doppler imag* OR pulmonary arter* n2 pressure OR lung* arter* n2 pressure
S4	(MH "Tomography, X-Ray Computed")
S5	(MH "Lung/RA") OR (MH "Lung Diseases/RA") OR (MH "Lung Diseases, Interstitial/RA")
S6	hrct OR comput* n3 tomograph* OR cat scan* OR ct scan*
S7	S1 or S2 or S3 or S4 or S5 or S6

Cochrane search terms

#1	MeSH descriptor Hypertension, Pulmonary, this term only
#2	MeSH descriptor Echocardiography explode all trees
#3	(echocardio* or tissue Doppler imag* or ((pulmonary or lung*) NEAR arter* NEAR/2 pressure)):ti,ab
#4	MeSH descriptor Tomography, X-Ray Computed explode all trees
#5	MeSH descriptor Lung, this term only with qualifier: RA
#6	MeSH descriptor Lung Diseases, this term only with qualifier: RA
#7	MeSH descriptor Lung Diseases, Interstitial, this term only with qualifier: RA
#8	(hrct or (comput* NEAR/3 tomograph*) or ((cat or ct) NEXT scan*)):ti,ab
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)

D.3.6 Psychosocial support

What is the specific type of psychosocial support and information for patients diagnosed with IPF?

Search constructed by combining the columns in the following table using the AND Boolean operator. For PsychInfo only the population terms were used.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
ILD	Psychosocial support		None, all study types considered	No date restriction. Search run up to 01/11/12

Psychosocial support search terms

Medline search terms

1	exp Information Services/ or exp Publications/ or Counseling/ or Directive Counseling/
2	Patient Education as Topic/ or Patient Education Handout/
3	"patient acceptance of health care"/ or exp patient satisfaction/
4	Communication/
5	exp Consumer Health Information/
6	exp Psychotherapy/
7	Social support/
8	((patient or patients) adj3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet* or website* or knowledge)).ti,ab.
9	(information* adj3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
10	((client* or patient* or user* or carer* or consumer* or customer*) adj2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*)).ti,ab.
11	(psycholog* or council* or counsel* or psychotherap* or psychosocial).ti,ab.
12	((support* or advice or advise) adj3 (telephone* or internet or program* or group*)).ti,ab.
13	or/1-12

Embase search terms

1	patient attitude/ or patient preference/ or patient satisfaction/ or consumer attitude/
2	consumer health information/
3	Information Service/ or Information center/ or Publication/ or Book/
4	Patient information/ or Patient education/
5	medical information/
6	health literacy/
7	exp *interpersonal communication/
8	exp Counseling/
9	exp psychotherapy/
10	psychosocial care/
11	*social support/
12	((patient or patients) adj3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet* or website* or knowledge)).ti,ab.
13	(information* adj3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
14	((client* or patient* or user* or carer* or consumer* or customer*) adj2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*)).ti,ab.
15	(psycholog* or council* or counsel* or psychotherap* or psychosocial).ti,ab.
16	((support* or advice or advise) adj3 (telephone* or internet or program*or group*)).ti,ab.

17	or/1-16

Cinahl search terms

S1	(MH "Information Services+") OR (MH "Counseling+") OR (MH "Patient Education") OR (MH "Patient Discharge Education") OR (MH "Health Education") OR (MH "Death Education") OR (MH "Patient Attitudes") OR (MH "Communication+")
S2	(MH "Consumer Health Information") OR (MH "Psychotherapy+")
S3	((patient or patients) n3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet* or website* or knowledge))
S4	(information* n3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*))
S5	((client* or patient* or user* or carer* or consumer* or customer*) n2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*))
S6	psycholog* or council* or counsel* or psychotherap* or psychosocial
S7	((support* or advice or advise) n3 (telephone* or internet or program* or group*))
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7

Cochrane search terms

#1	MeSH descriptor Information Services explode all trees
#2	MeSH descriptor Publications explode all trees
#3	MeSH descriptor Counseling, this term only
#4	MeSH descriptor Directive Counseling, this term only
#5	MeSH descriptor Patient Education as Topic, this term only
#6	MeSH descriptor Patient Acceptance of Health Care, this term only
#7	MeSH descriptor Patient Satisfaction explode all trees
#8	MeSH descriptor Communication, this term only
#9	MeSH descriptor Consumer Health Information explode all trees
#10	MeSH descriptor Psychotherapy explode all trees
#11	MeSH descriptor Social Support, this term only
#12	((patient or patients) NEAR/3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet* or website* or knowledge)):ti,ab
#13	(information* NEAR/3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)):ti,ab
#14	((client* or patient* or user* or carer* or consumer* or customer*) NEAR/2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*)):ti,ab
#15	(psycholog* or council* or counsel* or psychotherap* or psychosocial):ti,ab
#16	((support* or advice or advise) NEAR/3 (telephone* or internet or program* or group*)):ti,ab
#17	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)

D.3.7 Best supportive care/ patient review and follow up

Searches for the following three questions were run as one search:

What is the clinical and cost effectiveness of best supportive care (palliation of cough, breathlessness and fatigue, and oxygen management) in the symptomatic relief of patients with IPF?

How often should a patient with confirmed diagnosis of IPF be reviewed?

In which healthcare setting and by whom should a review appointment for patients with confirmed IPF be conducted?

Search constructed by combining the columns in the following table using the AND Boolean operator. For PsychInfo only the population terms were used.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
ILD	Best supportive care (BSC) or patient review		SRs, RCTs, observational (Medline and Embase only)	No date restriction. Search run up to 01/11/12

BSC/ patient review search terms

Medline search terms

1	exp oximetry/
2	Oxygen Inhalation Therapy/
3	Oxygen/
4	((oxygen or o2) adj3 (manag* or assess* or saturation* or sats or therap* or review* or ambulat* or nocturnal* or measur* or transcutaneous)).ti,ab.
5	(oximetr* or ptc02 or tcp02 or ltot).ti,ab.
6	or/1-5
7	Dyspnea/
8	(breathless* or dyspnea* or (short* adj2 breath*)).ti,ab.
9	or/7-8
10	Cough/
11	cough*.ti,ab.
12	or/10-11
13	Fatigue/
14	(fatigue* or lassitude).ti,ab.
15	or/13-14
16	Palliative Care/
17	(((best supportive or palliat*) adj2 (care or treat* or therap*)) or (symptom* adj2 (relie* or palliat*))).ti,ab.
18	or/16-17
19	((review or reviews or "follow up*" or follow-up* or "check up*" or check-up* or monit*) adj3 (patient* or appoint* or clinic* or gp or routine or regular or assess* or hospital* or primary care or consult*)).ti,ab.
20	((hospital or frequent or frequency or periodic* or standardiz* or standardis* or out-patient or patient-initiated or GP-initiated or rheumatologist-initiated) adj2 (review or reviews or "follow up*" or follow-up* or "check up*" or check-up*)).ti,ab.
21	or/19-20
22	6 or 9 or 12 or 15 or 18 or 21

Embase search terms

1	exp oximetry/
2	oxygen therapy/ or exp home oxygen therapy/
3	oxygen saturation/

4	*oxygen/
5	((oxygen or o2) adj3 (manag* or assess* or saturation* or sats or therap* or review* or ambulat* or nocturnal* or measur* or transcutaneous)).ti,ab.
6	(oximetr* or ptc02 or tcp02 or ltot).ti,ab.
7	or/1-6
8	(breathless* or dyspnea* or (short* adj2 breath*)).ti,ab.
9	*dyspnea/
10	or/8-9
11	cough*.ti,ab.
12	*coughing/
13	or/11-12
14	fatigue/ or exp lassitude/
15	(fatigue* or lassitude).ti,ab.
16	or/14-15
17	palliative therapy/
18	(((best supportive or palliat*) adj2 (care or treat* or therap*)) or (symptom* adj2 (relie* or palliat*))).ti,ab.
19	or/17-18
20	((review or reviews or "follow up*" or follow-up* or "check up*" or check-up* or monit*) adj3 (patient* or appoint* or clinic* or gp or routine or regular or assess* or hospital* or primary care or consult*)).ti,ab.
21	((hospital or frequent or frequency or periodic* or standardiz* or standardis* or out-patient or patient-initiated or GP-initiated or rheumatologist-initiated) adj2 (review or reviews or "follow up*" or follow-up* or "check up*" or check-up*)).ti,ab.
22	or/20-21
23	7 or 10 or 13 or 16 or 19 or 22

Cinahl search terms

S1	(MH "Oximetry+") OR (MH "Oxygen Therapy") OR (MH "Home Oxygen Therapy") OR (MH "Oxygen Saturation") OR (MH "Oxygen")
S2	((oxygen or o2) n3 (manag* or assess* or saturation* or sats or therap* or review* or ambulat* or nocturnal* or measur* or transcutaneous))
S3	oximetr* or ptc02 or tcp02 or ltot
S4	(MH "Dyspnea") OR (MH "Cough") OR (MH "Fatigue") OR (MH "Palliative Care") OR (MH "After Care")
S5	(breathless* or dyspnea* or (short* n2 breath*))
S6	cough* OR fatigue* OR lassitude
S7	(((best supportive or palliat*) n2 (care or treat* or therap*)) or (symptom* n2 (relie* or palliat*)))
S8	((review or reviews or "follow up*" or follow-up* or "check up*" or check-up* or monit*) n3 (patient* or appoint* or clinic* or gp or routine or regular or assess* or hospital* or primary care or consult*))
S9	((hospital or frequent or frequency or periodic* or standardiz* or standardis* or out-patient or patient-initiated or GP-initiated or rheumatologist-initiated) n2 (review or reviews or "follow up*" or follow-up* or "check up*" or check-up*))
S10	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9

Cochrane search terms

#1	MeSH descriptor Oximetry explode all trees

#2	MeSH descriptor Oxygen Inhalation Therapy, this term only
#3	MeSH descriptor Oxygen, this term only
#4	((oxygen or o2) NEAR/3 (manag* or assess* or saturation* or sats or therap* or review* or ambulat* or nocturnal* or measur* or transcutaneous)):ti,ab
#5	(oximetr* or ptc02 or tcp02 or ltot):ti,ab
#6	MeSH descriptor Dyspnea, this term only
#7	(breathless* or dyspnea* or (short* NEAR/2 breath*)):ti,ab
#8	MeSH descriptor Cough, this term only
#9	cough*:ti,ab
#10	MeSH descriptor Fatigue, this term only
#11	(fatigue* or lassitude):ti,ab
#12	MeSH descriptor Palliative Care, this term only
#13	(((best supportive or palliat*) NEAR/2 (care or treat* or therap*)) or (symptom* NEAR/2 (relie* or palliat*))):ti,ab
#14	((review or reviews or "follow up*" or follow-up* or "check up*" or check-up* or monit*) NEAR/3 (patient* or appoint* or clinic* or gp or routine or regular or assess* or hospital* or primary care or consult*)):ti,ab
#15	((hospital or frequent or frequency or periodic* or standardiz* or standardis* or out-patient or patient-initiated or GP-initiated or rheumatologist-initiated) NEAR/2 (review or reviews or "follow up*" or follow-up* or "check up*" or check-up*)):ti,ab
#16	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)

D.3.8 Pulmonary rehabilitation

Searches for the following two questions were run as one search:

What are the benefits of pulmonary rehabilitation programmes for patients with confirmed IPF?

What is the optimal course content, setting and duration for patients referred for pulmonary rehab programmes?

Search constructed by combining the columns in the following table using the AND Boolean operator. For PsychInfo only the population terms were used.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
ILD	Pulmonary rehabilitation		None, all study types considered	No date restriction. Search run up to 01/11/12

Pulmonary rehabilitation search terms

Medline search terms

1	(fatigue severity scale* or visual analog* scale*).ti,ab.
2	(Borg adj2 scale*).ti,ab.
3	((Dyspn?ea or illness) adj index).ti,ab.
4	(Daily adj2 activit* adj2 (life or living)).ti,ab.
5	(Exercise or Treadmill or bicycle or stepper or weights or ergometer or walk*).ti,ab.
6	((Physical or aerobic or endurance or strength or fitness or resistance) adj2 (activit* or train* or condition* or program* or regime*)).ti,ab.

7	((minute walk adj (test or distance)) or 6MWT or 6MWD).ti,ab.
8	(cycle ergometry or ICET).ti,ab.
9	Shuttle walk*.ti,ab.
10	((Pulmonary adj2 rehabilitat*) or (rehabilitat* adj2 program*)).ti,ab.
11	Written disclosure therap*.ti,ab.
12	(psycholog* or council* or counsel* or psychotherap*).ti,ab.
13	((Emotional or psychosocial) adj2 support).ti,ab.
14	((patient* or carer*) adj2 (information or education* or knowledge)).ti,ab.
15	((patient* or carer*) adj5 (leaflet* or pamphlet* or booklet* or website* or web site*)).ti,ab.
16	((multifactor* or multifacet* or managed care) adj program*).ti,ab.
17	(Diet* or nutrition*).ti,ab.
18	(((Respiratory disease or George* respiratory) adj questionnaire*) or sgrq).ti,ab.
19	(WHOQOL-100 or whoQoL100).ti,ab.
20	(Support adj group*).ti,ab.
21	(disease adj management adj program*).ti,ab.
22	*Exercise Test/
23	exp Exercise Tolerance/
24	exp Exercise Movement Techniques/
25	*Exercise/
26	*Walking/
27	Physical endurance/
28	Exercise therapy/
29	Rehabilitation/
30	Rehabilitation centers/
31	Severity of illness index/
32	Activities of daily living/
33	Managed care programs/
34	Patient Education as Topic/
35	exp Consumer Health Information/
36	Access to Information/
37	Information services/
38	Pamphlets/
39	Counseling/
40	exp Psychotherapy/
41	exp diet/
42	exp nutrition therapy/
43	or/1-42

Embase search terms

1	(fatigue severity scale* or visual analog* scale*).ti,ab.
2	(Borg adj2 scale*).ti,ab.
3	((Dyspn?ea or illness) adj index).ti,ab.
4	(Daily adj2 activit* adj2 (life or living)).ti,ab.
5	(Exercise or Treadmill or bicycle or stepper or weights or ergometer or walk*).ti,ab.
6	((Physical or aerobic or endurance or strength or fitness or resistance) adj2 (activit* or train*

	or condition* or program* or regime*)).ti,ab.
7	((minute walk adj (test or distance)) or 6MWT or 6MWD).ti,ab.
8	(cycle ergometry or ICET).ti,ab.
9	Shuttle walk*.ti,ab.
10	((Pulmonary adj2 rehabilitat*) or (rehabilitat* adj2 program*)).ti,ab.
11	Written disclosure therap*.ti,ab.
12	(psycholog* or council* or counsel* or psychotherap*).ti,ab.
13	((Emotional or psychosocial) adj2 support).ti,ab.
14	((patient* or carer*) adj2 (information or education* or knowledge)).ti,ab.
15	((patient* or carer*) adj5 (leaflet* or pamphlet* or booklet* or website* or web site*)).ti,ab.
16	((multifactor* or multifacet* or managed care) adj program*).ti,ab.
17	(Diet* or nutrition*).ti,ab.
18	(((Respiratory disease or George* respiratory) adj questionnaire*) or sgrq).ti,ab.
19	(WHOQOL-100 or whoQoL100).ti,ab.
20	(Support adj group*).ti,ab.
21	(disease adj management adj program*).ti,ab.
22	*Exercise/
23	*Exercise test/
24	exp Exercise tolerance/
25	Muscle training/
26	exp Pulmonary rehabilitation/
27	Rehabilitation/
28	Pulmonary Rehabilitation Program/
29	*Walking/
30	Rehabilitation center/
31	Daily life activity/
32	patient education/
33	patient information/
34	information service/
35	medical information/
36	health literacy/
37	exp Counseling/
38	exp psychotherapy/
39	*nutrition/
40	exp diet/
41	exp diet therapy/
42	or/1-41

Cinahl search terms

S1	Exercise or Treadmill or bicycle or stepper or weights or ergometer or walk*
S2	psycholog* or council* or counsel* or psychotherap* or psychosocial or emotional or pulmonary rehabilitat*
S3	(MH "Rehabilitation, Pulmonary+") OR (MH "Rehabilitation Centers+") OR (MH "Patient Education")
S4	(patient* n2 information) or (patient* n2 education*) or (patient* n2 knowledge*)
S5	(MH "Nutrition Education") OR diet* OR nutrition*

S6	(MH "Nutritional Counseling") OR (MH "Counseling") OR shuttle walk*
S7	(MH "Diet") OR (MH "Nutrition") OR fatigue severity scale*
S8	visual analog* scale* OR Borg N2 scale OR daily N2 activit*
S9	written disclosure therap* OR managed care program* OR (MH "Managed Care Programs")
S10	(MH "Walking") OR (MH "Activities of Daily Living+") OR (MH "Exercise+") OR (MH "Physical Endurance+")
S11	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10

Cochrane search terms

#1	(Exercis* or Treadmill or bicycle or stepper or weights or ergometer or walk*):ti,ab
#2	((Physical or aerobic or endurance or strength or fitness or resistance) NEAR/2 (activit* or train* or condition* or program* or regime*)):ti,ab
#3	(6MWT or 6MWD):ti,ab
#4	(minute walk NEXT (test or distance)):ti,ab
#5	((cycle NEXT ergometry) or ICET):ti,ab
#6	(Shuttle NEXT walk*):ti,ab
#7	((Pulmonary NEAR/2 rehabilitat*) or (rehabilitat* NEAR/2 program*)):ti,ab
#8	(Written NEXT disclosure NEXT therap*):ti,ab
#9	(psycholog* or council* or counsel* or psychotherap*):ti,ab
#10	((Emotional or psychosocial) NEAR/2 support):ti,ab
#11	((multifactor* or multifacet* or managed care) NEXT program*):ti,ab
#12	(Diet* or nutrition*):ti,ab
#13	(((patient* or carer*) NEAR/2 (information or education* or knowledge)) AND rehabilitat*):ti,ab
#14	(((patient* or carer*) NEAR/5 (leaflet* or pamphlet* or booklet* or website* or web site*) AND rehabilitat*)):ti,ab
#15	MeSH descriptor Exercise Test, this term only
#16	MeSH descriptor Exercise Tolerance, this term only
#17	MeSH descriptor Exercise Movement Techniques explode all trees
#18	MeSH descriptor Exercise explode all trees
#19	MeSH descriptor Walking explode all trees
#20	MeSH descriptor Physical Endurance explode all trees
#21	MeSH descriptor Exercise Therapy explode all trees
#22	MeSH descriptor Rehabilitation explode all trees
#23	MeSH descriptor Managed Care Programs, this term only
#24	MeSH descriptor Patient Education as Topic explode all trees
#25	MeSH descriptor Consumer Health Information explode all trees
#26	MeSH descriptor Access to Information explode all trees
#27	MeSH descriptor Information Services explode all trees
#28	MeSH descriptor Pamphlets explode all trees
#29	MeSH descriptor Counseling explode all trees
#30	MeSH descriptor Psychotherapy explode all trees
#31	MeSH descriptor Diet explode all trees
#32	MeSH descriptor Nutrition Therapy explode all trees
#33	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26

	OR #27 OR #28 OR #29 OR #30 OR #31 OR #32)

D.3.9 Pharmacological interventions

Searches for the following two questions were run as one search:

Which drug should be initiated first, for how long, and what combination in the treatment of IPF?

(Sub-question) What is the clinical and cost effectiveness of pharmacological interventions to manage patients with suspected or confirmed IPF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
IPF	Pharmacological interventions		SRs, RCTs (Medline and Embase only)	No date restriction. Search run up to 01/11/12

Pharmacological intervention search terms

Medline search terms

1	Acetylcysteine/
2	(acetylcystein* or acetyl cystein* or acetadote or parvolex).ti,ab.
3	Azathioprine/
4	exp Immunosuppressive Agents/
5	(azathioprine or imuran or azasan or immunosuppress*).ti,ab.
6	(ambrisentan or volibris or letairis or bosentan or tracleer).ti,ab.
7	Glucocorticoids/ or Adrenal cortex hormones/ or Pregnadienetriols/ or Pregnenediones/
8	Prednisolone/ or betamethasone/ or cortisone/ or dexamethasone/ or hydrocortisone/ or methylprednisolone/ or prednisone/ or triamcinolone/ or beclomethasone/ or budesonide/
9	(Prednisolone or prednisone or deltacotril or (pred adj forte) or methylprednisolone or depo medrol or lodotra or Deltastab or betamethasone or betnelan or betnesol).ti,ab.
10	(cortisone or deflazacort or calcort or dexamethasone or hydrocortisone).ti,ab.
11	(triamcinolone or Nasacort or adcortyl or kenalog or triderm or triacet or trivaris or triesence).ti,ab.
12	(Efcortesol or (Solu adj Cortef) or Medrone or (Solu adj Medrone) or Hydrocortistab or (Depo adj Medrone) or Adcortyl).ti,ab.
13	(beclometasone or beclomethasone or qvar or fostair or clenil or asmabec or beconase or pulvinal or becodisks or budesonide or budelin or budenofalk or pulmicort or symbicort or rhinocort or entocort).ti,ab.
14	(ciclesonide or alvesco or omnaris or fluticasone or flixotide or seretide or evohaler or veramyst or flovent or flonase or cutivate or advair or avamys or flixonase or pirinase or asmanex or elocon or nasonex).ti,ab.
15	(Glucocorticoid* or Corticosteroid* or Adrenal cortex hormone*).ti,ab.
16	Trimethoprim-Sulfamethoxazole Combination/
17	((trimethoprim adj2 sulfamethoxazole) or co trimoxazole or septrin).ti,ab.
18	(arzip or cellcept or mycophenolic or myfortic or mycophenolate).ti,ab.
19	mycophenolic acid/
20	Warfarin/
21	warfarin.ti,ab.

22	anticoagulants/ or antithrombins/
23	exp Acenocoumarol/
24	exp Phenindione/
25	exp Coumarins/
26	phenprocoumon/
27	(acenocoumarol or nicoumalone or phenprocoumon or phenindione or nicoumalone or acenocoumarin or sinthrome or sintrom or coumadin or coumarin* or hydroxycoumarin* or (anti adj coagulant*)).ti,ab.
28	Proton pump inhibitors/
29	(proton adj3 pump* adj3 (inhibitor* or antagonist*)).ti,ab.
30	Omeprazole/
31	(omeprazole or prilosec or nexium or esomeprazole or vimovo or losec or pantoprazole or protium or protonix or lansoprazole or prevacid or zoton or rabeprazole or pariet).ti,ab.
32	(sildenafil or viagra or revatio).ti,ab.
33	vasodilator*.ti,ab.
34	*Vasodilator Agents/
35	((phosphodiesterase adj2 inhibitor*) or avanafil or beminafil or dasantafil or gisadenafil or lodenafil or mirodenafil or tadalafil or udenafil or vardenafil).ti,ab.
36	or/1-35

Embase search terms

1	acetylcysteine/
2	(acetylcystein* or acetyl cystein* or acetadote or parvolex).ti,ab.
3	(azathioprine or imuran or azasan or immunosuppress*).ti,ab.
4	azathioprine/ or immunosuppressive agent/
5	(ambrisentan or volibris or letairis or bosentan or tracleer).ti,ab.
6	Glucocorticoid/
7	Corticosteroid/
8	Corticosteroid derivative/
9	Pregnane derivative/
10	Prednisolone/ or betamethasone/ or cortisone/deflazacort or dexamethasone/ or hydrocortisone/ or methylprednisolone/ or prednisone/ or triamcinolone/ or beclometasone/ or beclometasone diproprionate/ or beclometasone dipropionate plus salbutamol/ or budesonide/ or ciclesonide/
11	(Prednisolone or prednisone or deltacotril or (pred adj forte) or methylprednisolone or depo medrol or lodotra or Deltastab or betamethasone or betnelan or betnesol).ti,ab.
12	(cortisone or deflazacort or calcort or dexamethasone or hydrocortisone).ti,ab.
13	(triamcinolone or Nasacort or adcortyl or kenalog or triderm or triacet or trivaris or triesence).ti,ab.
14	(Efcortesol or (Solu adj Cortef) or Medrone or (Solu adj Medrone) or Hydrocortistab or (Depo adj Medrone) or Adcortyl).ti,ab.
15	(beclometasone or beclomethasone or qvar or fostair or clenil or asmabec or beconase or pulvinal or becodisks or budesonide or budelin or budenofalk or pulmicort or symbicort or rhinocort or entocort).ti,ab.
16	(ciclesonide or alvesco or omnaris or fluticasone or flixotide or seretide or evohaler or veramyst or flovent or flonase or cutivate or advair or avamys or flixonase or pirinase or asmanex or elocon or nasonex).ti,ab.
17	(Glucocorticoid* or Corticosteroid* or Adrenal cortex hormone*).ti,ab.

18	((trimethoprim adj2 sulfamethoxazole) or co trimoxazole or septrin).ti,ab.
19	cotrimoxazole/
20	(arzip or cellcept or mycophenolic or myfortic or mycophenolate).ti,ab.
21	mycophenolic acid 2 morpholinoethyl ester/
22	warfarin/
23	warfarin.ti,ab.
24	(acenocoumarol or nicoumalone or phenindione or nicoumalone or acenocoumarin or sinthrome or sintrom or coumadin or coumarin* or hydroxycoumarin* or (anti adj coagulant*)).ti,ab.
25	exp coumarin/
26	anticoagulant agent/
27	exp phenindione/
28	exp acenocoumarol/
29	phenprocoumon/
30	exp coumarin anticoagulant/
31	phenprocoumon.ti,ab.
32	exp Proton pump inhibitor/
33	(proton adj3 pump* adj3 (inhibitor* or antagonist*)).ti,ab.
34	Esomeprazole/
35	Omeprazole/
36	Lansoprazole/
37	Rabeprazole/
38	pantoprazole/
39	(omeprazole or prilosec or nexium or esomeprazole or vimovo or losec or pantoprazole or protium or protonix or lansoprazole or prevacid or zoton or rabeprazole or pariet).ti,ab.
40	(sildenafil or viagra or revatio).ti,ab.
41	*sildenafil/
42	*phosphodiesterase V inhibitor/
43	phosphodiesterase v inhibitor/ or *avanafil/ or *beminafil/ or *dasantafil/ or *gisadenafil/ or *lodenafil/ or *mirodenafil/ or *sildenafil/ or *sildenafil nitrate/ or *tadalafil/ or *udenafil/ or *vardenafil/
44	((phosphodiesterase adj2 inhibitor*) or avanafil or beminafil or dasantafil or gisadenafil or lodenafil or mirodenafil or tadalafil or udenafil or vardenafil).ti,ab.
45	or/1-44

Cochrane search terms

#1	(acetylcystein* or (acetyl NEXT cystein*) or acetadote or parvolex):ti,ab
#2	MeSH descriptor Acetylcysteine explode all trees
#3	(azathioprine or imuran or azasan or immunosuppress*):ti,ab
#4	MeSH descriptor Azathioprine explode all trees
#5	MeSH descriptor Immunosuppressive Agents explode all trees
#6	(ambrisentan or volibris or letairis or bosentan or tracleer):ti,ab,kw
#7	MeSH descriptor Glucocorticoids explode all trees
#8	MeSH descriptor Adrenal Cortex Hormones explode all trees
#9	MeSH descriptor Pregnadienetriols explode all trees
#10	MeSH descriptor Pregnenediones explode all trees

#11	MeSH descriptor Prednisolone explode all trees
#12	MeSH descriptor Betamethasone explode all trees
#13	MeSH descriptor Cortisone explode all trees
#14	MeSH descriptor Dexamethasone explode all trees
#15	MeSH descriptor Hydrocortisone explode all trees
#16	MeSH descriptor Methylprednisolone explode all trees
#17	MeSH descriptor Prednisone explode all trees
#18	MeSH descriptor Triamcinolone explode all trees
#19	MeSH descriptor Beclomethasone explode all trees
#20	MeSH descriptor Budesonide explode all trees
#21	(Prednisolone or prednisone or deltacotril or (pred adj forte) or methylprednisolone or (depo medrol) or lodotra or Deltastab or betamethasone or betnelan or betnesol):ti,ab
#22	(cortisone or deflazacort or calcort or dexamethasone or hydrocortisone):ti,ab
#23	(triamcinolone or Nasacort or adcortyl or kenalog or triderm or triacet or trivaris or triesence):ti,ab
#24	(Efcortesol or (Solu NEXT Cortef) or Medrone or (Solu NEXT Medrone) or Hydrocortistab or (Depo NEXT Medrone) or Adcortyl):ti,ab
#25	(beclometasone or beclomethasone or qvar or fostair or clenil or asmabec or beconase or pulvinal or becodisks or budesonide or budelin or budenofalk or pulmicort or symbicort or rhinocort or entocort):ti,ab
#26	(ciclesonide or alvesco or omnaris or fluticasone or flixotide or seretide or evohaler or veramyst or flovent or flonase or cutivate or advair or avamys or flixonase or pirinase or asmanex or elocon or nasonex):ti,ab
#27	(Glucocorticoid* or Corticosteroid* or (Adrenal cortex hormone*)):ti,ab
#28	((trimethoprim adj2 sulfamethoxazole) or (co trimoxazole)):ti,ab
#29	MeSH descriptor Trimethoprim-Sulfamethoxazole Combination explode all trees
#30	(arzip or cellcept or mycophenolic or myfortic or mycophenolate):ti,ab
#31	MeSH descriptor Mycophenolic Acid explode all trees
#32	(warfarin):ti,ab,kw
#33	MeSH descriptor Warfarin, this term only
#34	(acenocoumarol or nicoumalone or phenprocoumon or phenindione or nicoumalone or acenocoumarin or sinthrome or sintrom or coumadin or coumarin* or hydroxycoumarin* or (anti adj coagulant*)):ti,ab
#35	MeSH descriptor Anticoagulants explode all trees
#36	MeSH descriptor Antithrombins explode all trees
#37	MeSH descriptor Acenocoumarol explode all trees
#38	MeSH descriptor Phenindione, this term only
#39	MeSH descriptor Coumarins explode all trees
#40	MeSH descriptor Phenprocoumon, this term only
#41	MeSH descriptor Proton Pump Inhibitors explode all trees
#42	MeSH descriptor Omeprazole explode all trees
#43	(omeprazole or prilosec or nexium or esomeprazole or vimovo or losec or pantoprazole or protium or protonix or lansoprazole or prevacid or zoton or rabeprazole or pariet):ti,ab
#44	((phosphodiesterase adj2 inhibitor*) or avanafil or beminafil or dasantafil or gisadenafil or lodenafil or mirodenafil or tadalafil or udenafil or vardenafil or sildenafil or viagra or revatio or vasodilator*):ti,ab,kw
#45	MeSH descriptor Vasodilator Agents explode all trees

#46	(proton NEAR/3 pump* NEAR/3 (inhibitor* or antagonist*)):ti,ab
#47	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46)

D.3.10 Pharmacological interventions: adverse events

Which measures can be taken to minimize the occurrence/severity of adverse events when undergoing pharmacological treatment for IPF?"

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
IPF OR Azazthioprine	TPMT		None, all study types considered	No date restriction. Search run up to 01/11/12

Azathioprine search terms

Medline search terms

1	(az#thiopri* or azasan or azamune or im?uran or imure#).ti,ab.
2	exp Azathioprine/
3	1 or 2

Embase search terms

1	exp azathioprine/
2	(az#thiopri* or azasan or azamune or im?uran or imure#).ti,ab.
3	1 or 2

Cochrane search terms

#1	(az?thiopri* or azasan or azamune or imuran or immuran or imurel or imurek or imuren):ti,ab
#2	MeSH descriptor Azathioprine explode all trees
#3	#1 OR #2

TMPT search terms

Medline search terms

1	*Methyltransferases/
2	((thiopurine adj2 methyltransferase) or (methyl adj2 methyl transferase) or tpmt).ti,ab.
3	1 or 2

Embase search terms

1	exp thiopurine methyltransferase/ or *methyltransferase/
2	((thiopurine adj2 methyltransferase) or (thiopurine adj2 methyl transferase) or tpmt).ti,ab.
3	1 or 2

Cochrane search terms

#1	((thiopurine NEAR/2 methyl) NEXT transferase):ti,ab
#2	tpmt:ti,ab
#3	(thiopurine NEAR/2 methyltransferase):ti,ab

#4	MeSH descriptor Methyltransferases, this term only
#5	#1 OR #2 OR #3 OR #4

D.3.11 Lung transplantation

At what time points in the IPF care pathway should a patient be considered for referral for lung transplantation?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
IPF	Lung transplantation		SRs, RCTs, observsational (Medline and Embase only)	No date restriction. Search run up to 01/11/12

Lung transplantation search terms

Medline search terms

1	lung transplantation/
2	(lung* adj3 (transplant* or graft*)).ti,ab.
3	or/1-2
4	"referral and consultation"/
5	time factors/
6	(prognos* or time or timing or early or earlier or late or later or refer* or consult* or criteri* or indicat* or assess*).ti,ab.
7	or/4-6
8	3 and 7

Embase search terms

1	*lung transplantation/
2	(lung* adj3 (transplant* or graft*)).ti,ab.
3	or/1-2
4	*patient referral/
5	time/
6	(prognos* or time or timing or early or earlier or late or later or refer* or consult* or criteri* or indicat* or assess*).ti,ab.
7	or/4-6
8	3 and 7

Cochrane search terms

#1	MeSH descriptor Lung Transplantation, this term only
#2	(lung* NEAR/3 (transplant* or graft*)):ti,ab
#3	(#1 OR #2)

D.3.12 Ventilation

In acute or acute-on chronic respiratory failure in patients with IPF, what is the value of non-invasive and invasive ventilation?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
IPF	Ventilation		SRs, RCTs, observational (Medline and Embase only)	No date restriction. Search run up to 01/11/12

Ventilation search terms

Medline search terms

1	exp Respiration, Artificial/
2	exp Ventilators, Mechanical/
3	((ventilat* or respirat*) adj2 (mechanical* or artificial* or assist* or invasive or noninvasive or non-invasive)).ti,ab.
4	((pressure support or high frequenc* or jet or oscillat* or liquid) adj1 ventilat*).ti,ab.
5	(bipap or nippv or nppv or niv or niav or cpap or aprv or ippb or ippv or peep or ipap or epap).ti,ab.
6	(positive airway pressure or (positive pressure adj (ventilati* or breath*)) or airway pressure release ventilation or positive end expiratory pressure).ti,ab.
7	(novalung or ecmo or (extracorporeal* adj2 membrane* adj2 oxygenat*)).ti,ab.
8	extracorporeal membrane oxygenation/
9	Oxygenators, Membrane/
10	or/1-9

Embase search terms

1	exp *artificial ventilation/
2	exp ventilator/
3	((ventilat* or respirat*) adj2 (mechanical* or artificial* or assist* or invasive or noninvasive or non-invasive)).ti,ab.
4	((pressure support or high frequenc* or jet or oscillat* or liquid) adj1 ventilat*).ti,ab.
5	(bipap or nippv or nppv or niv or niav or cpap or aprv or ippb or ippv or peep or ipap or epap).ti,ab.
6	(positive airway pressure or (positive pressure adj (ventilati* or breath*)) or airway pressure release ventilation or positive end expiratory pressure).ti,ab.
7	extracorporeal oxygenation/
8	oxygenator/
9	(novalung or ecmo or (extracorporeal* adj2 membrane* adj2 oxygenat*)).ti,ab.
10	or/1-9

Cochrane search terms

#1	MeSH descriptor Respiration, Artificial explode all trees
#2	MeSH descriptor Ventilators, Mechanical explode all trees
#3	((ventilat* or respirat*) NEAR/2 (mechanical* or artificial* or assist* or invasive or noninvasive or non-invasive)):ti,b
#4	((pressure support or high frequenc* or jet or oscillat* or liquid) NEAR ventilat*):ti,ab
#5	(bipap or nippv or nppv or niv or niav or cpap or aprv or ippb or ippv or peep or ipap or epap):ti,ab
#6	(positive airway pressure or ((positive pressure) NEXT (ventilati* or breath*)) or airway pressure release ventilation or positive end expiratory pressure):ti,ab
#7	MeSH descriptor Extracorporeal Membrane Oxygenation, this term only

#8	MeSH descriptor Oxygenators, Membrane, this term only
#9	(novalung or ecmo or (extracorporeal* NEAR/2 membrane* NEAR/2 oxygenat*)):ti,ab
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)

D.4 Economics search

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
ILD			Economic, economic modelling, quality of life, disease progression (Medline and Embase only)	No date restriction. Search run up to 01/11/12. Economic filter in Medline and Embase limited to 2010 - 01/11/12

CRD search terms

#1	MeSH DESCRIPTOR Lung Diseases, Interstitial EXPLODE ALL TREES WITH QUALIFIER undefined
#2	MeSH DESCRIPTOR Pulmonary Fibrosis EXPLODE ALL TREES WITH QUALIFIER undefined
#3	(interstitial near pneumonia*) IN NHSEED, HTA
#4	(interstitial near lung disease*) IN NHSEED, HTA
#5	(pulmonary near fibros*) IN NHSEED, HTA
#6	(alveoliti*) IN NHSEED, HTA
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6

HEED search terms

1	ax=interstitial
2	ax=pulmonary AND fibros*
3	ax=alveoliti*
4	ax=Pneumoconiosis
5	ax=Pneumonitis
6	ax=Sarcoidosis
7	ax=Wegener Granulomatosis
8	ax=lung AND fibros*
9	ax=organizing AND pneumonia
10	cs=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

Appendix E: Forest plots

E.1 Diagnosis

The data from these studies were not meta- analysable therefore forest plots for these outcomes could not be provided; see the clinical evidence profile and the evidence tables for further information

E.2 Prognosis

Note: For graphical purposes only, results have been presented in forest plots.

- *Only the results of the multivariable analysis have been reported in evidence tables and included in the final analysis.*
- *Inversed hazard ratios were calculated to present declines of PFT measures/ predicted values*
- *Hazard ratios were also calculated per 5% decline for FVC and per 10% decline for DLCO*

(See Appendix I for calculations of standard errors from hazard ratios, risk ratios and odds ratios)

Please note evidence from the same dataset was used for DuBois201[118], Dubois2011A[117] and DuBois2011B[121],

E.2.1 Serial pulmonary function tests

Figure 1: FVC per 5% predicted declines in patients with IPF at baseline; Mortality/ survival (time to event)

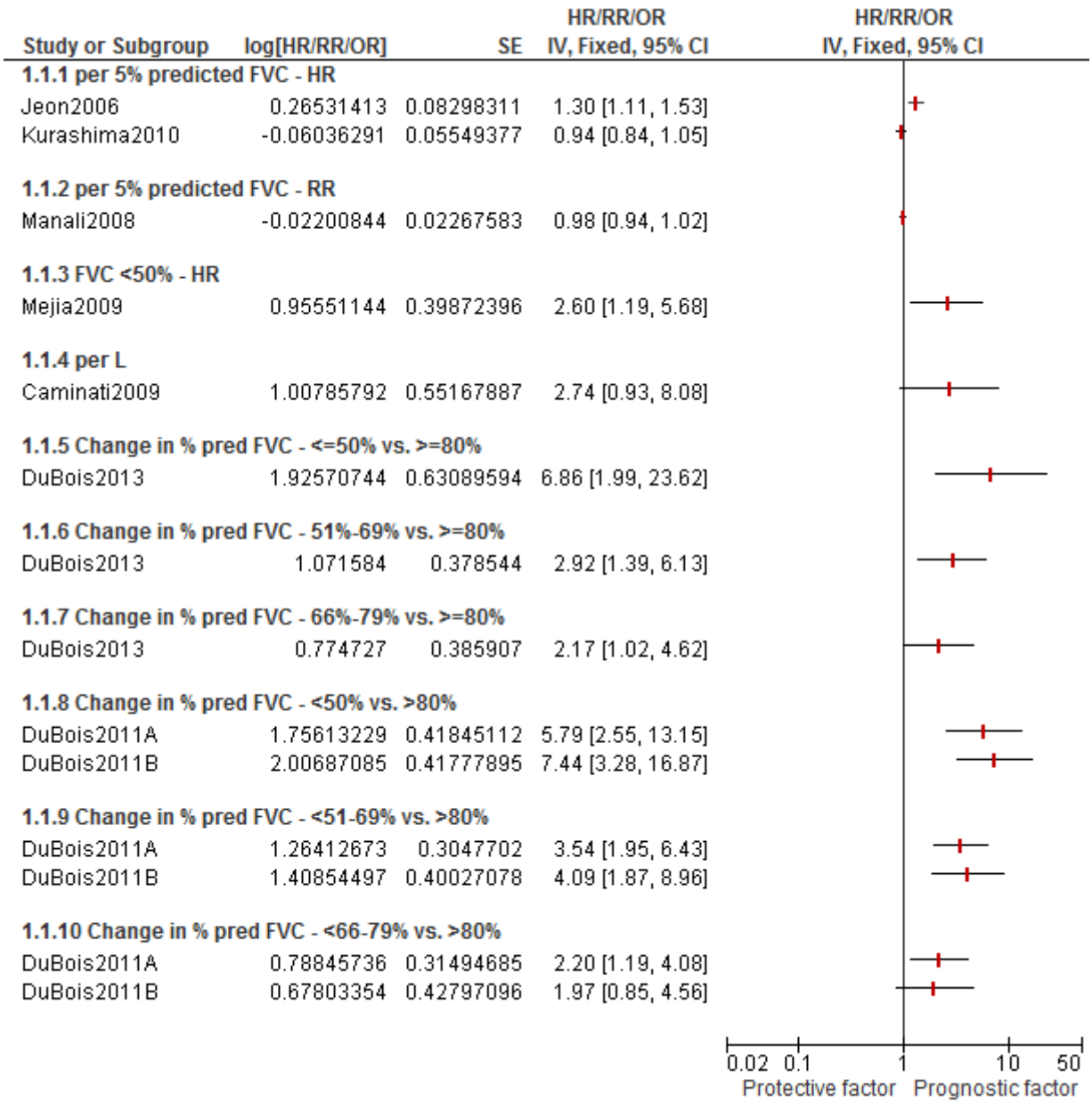


Figure 2: Relative declines in mortality/survival (time to event)

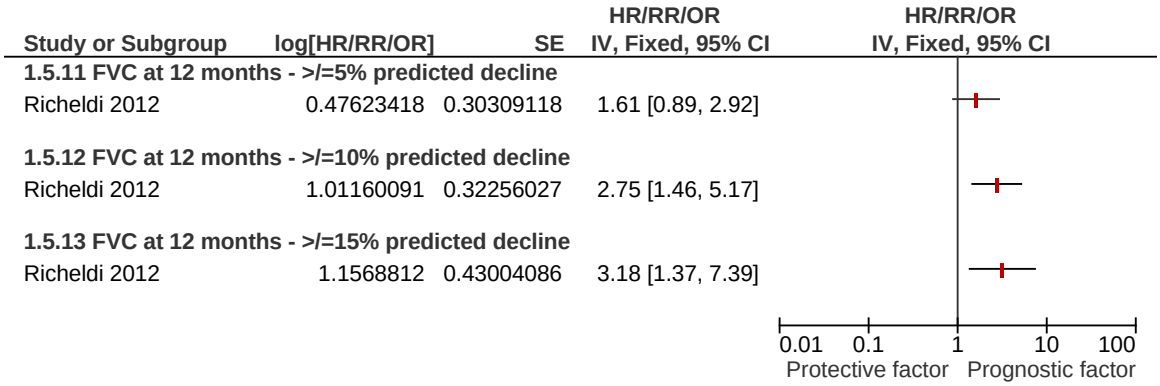


Figure 3: DLCO per 10% predicted declines in patients with IPF at baseline; Mortality/ survival (time to event)

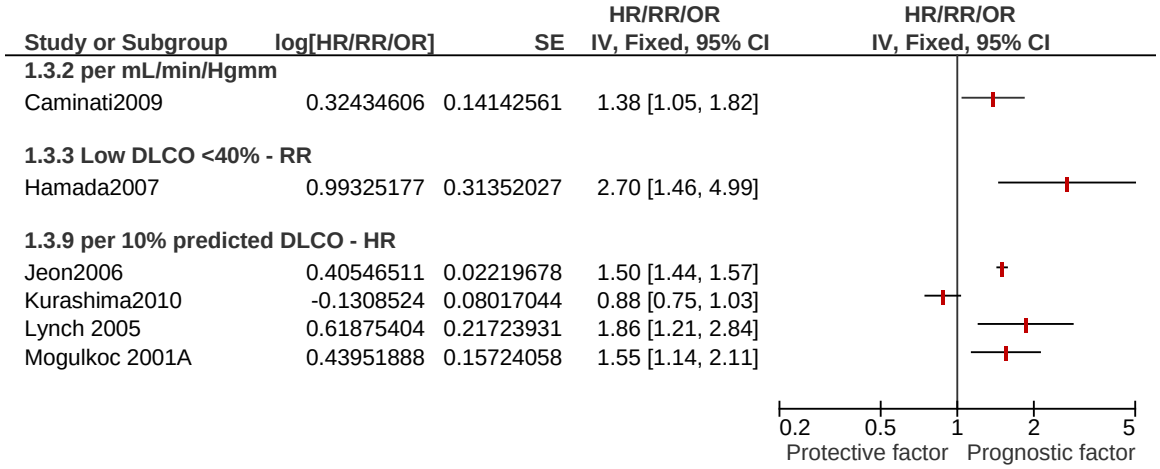


Figure 4: Absolute declines in FVC in patients with IPF; Mortality/ survival (time to event)

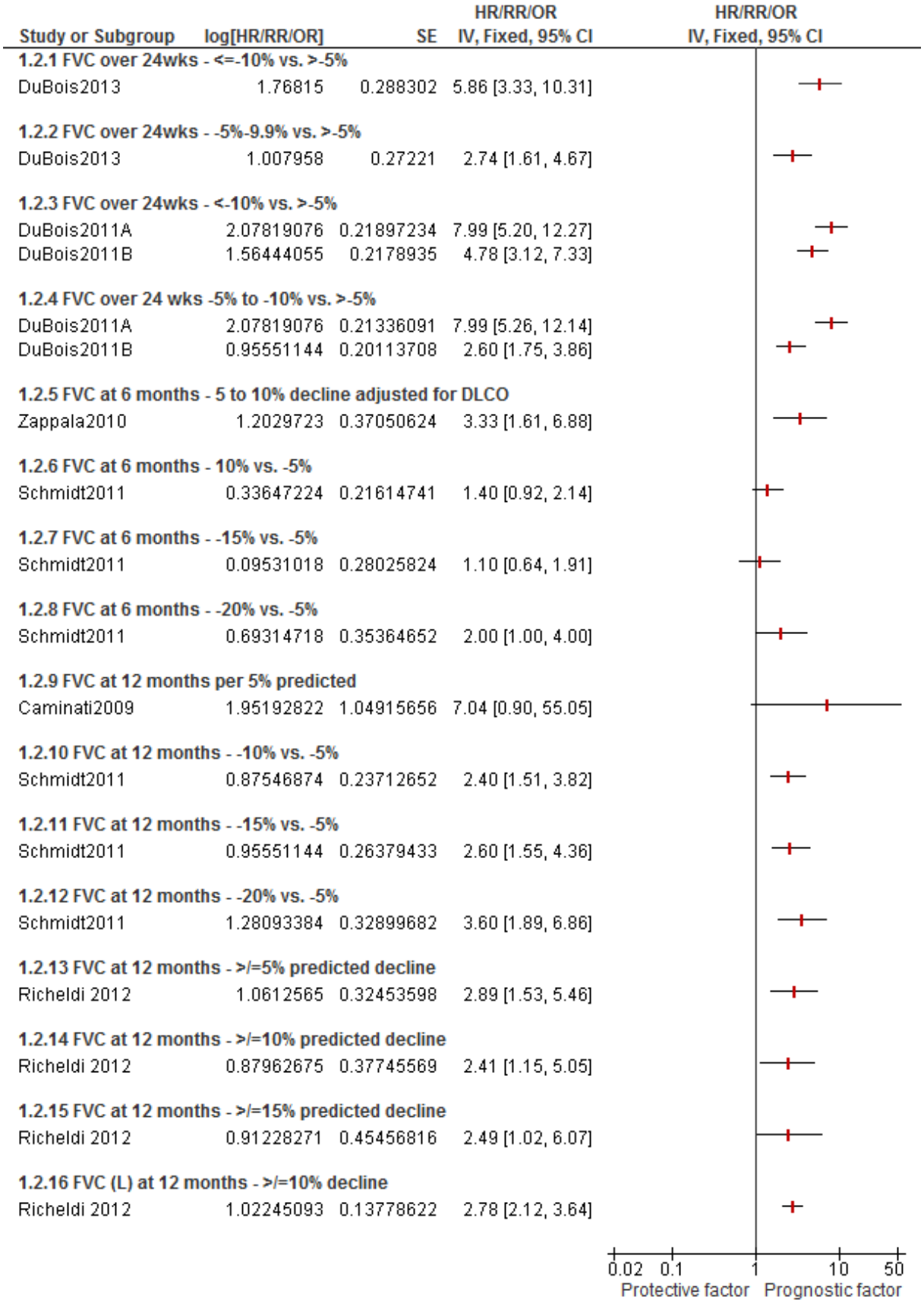


Figure 5: Absolute declines in DLCO in patients with IPF; mortality/ survival (time to event)

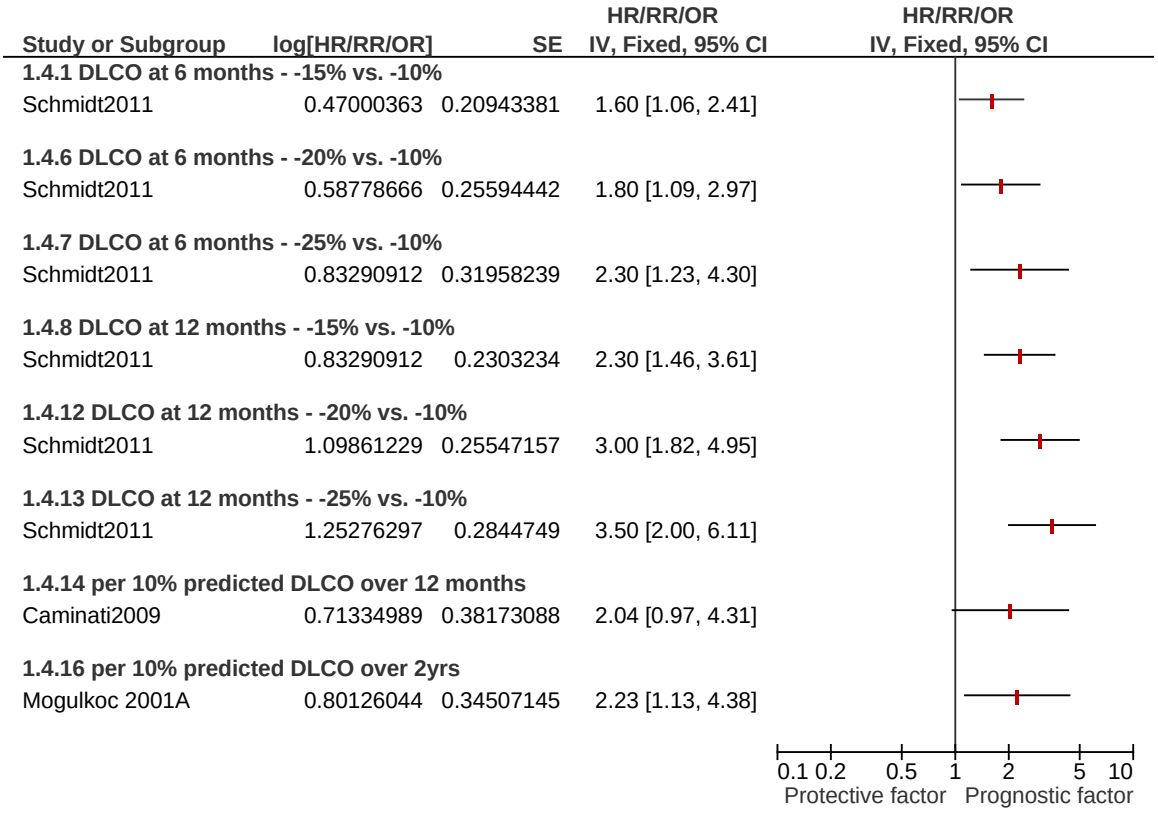


Figure 6: Baseline oxygen saturation in patients with IPF; mortality/ survival (time to event)

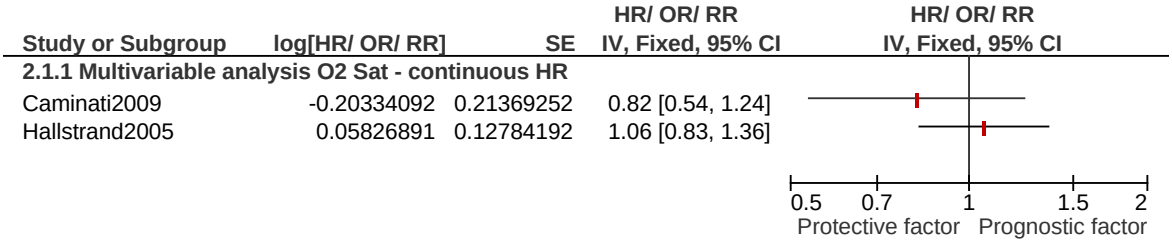


Figure 7: Absolute change in oxygen saturation at 12 months; mortality/ survival (time to event)

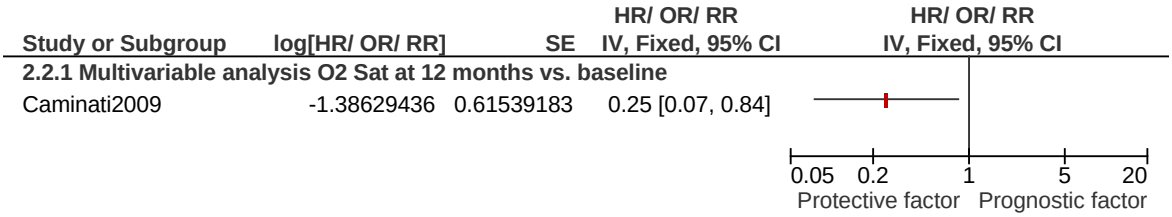
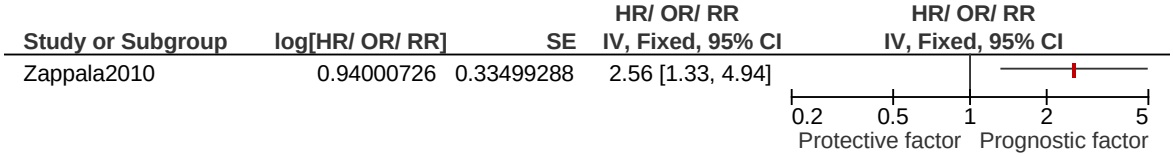


Figure 8: Percentage predicted decline in FVC (5-10%) adjusted for DLCO compared to stable disease in patients with IPF; progression free survival



E.2.2 Sub maximal exercise testing

Figure 9: Baseline 6MWD: mortality

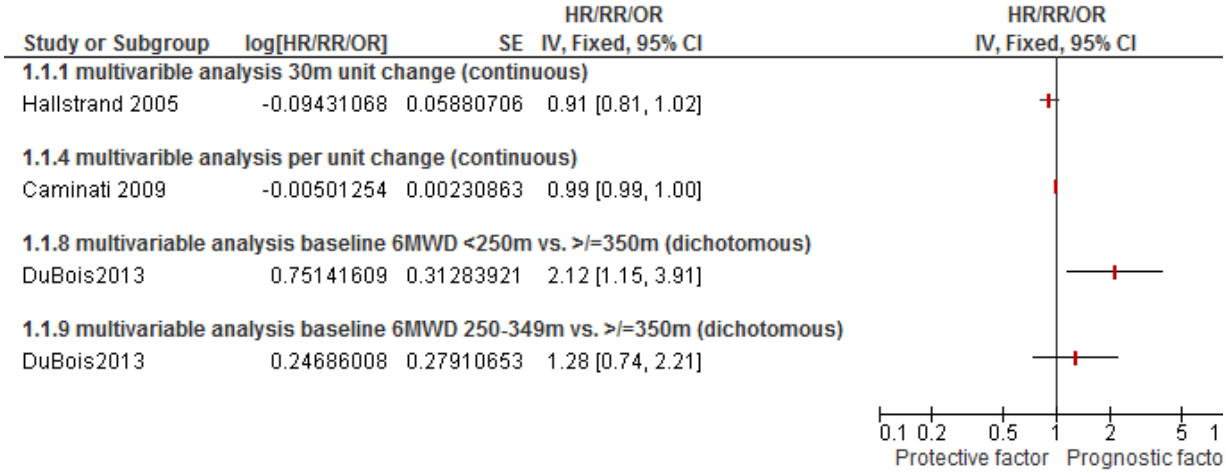
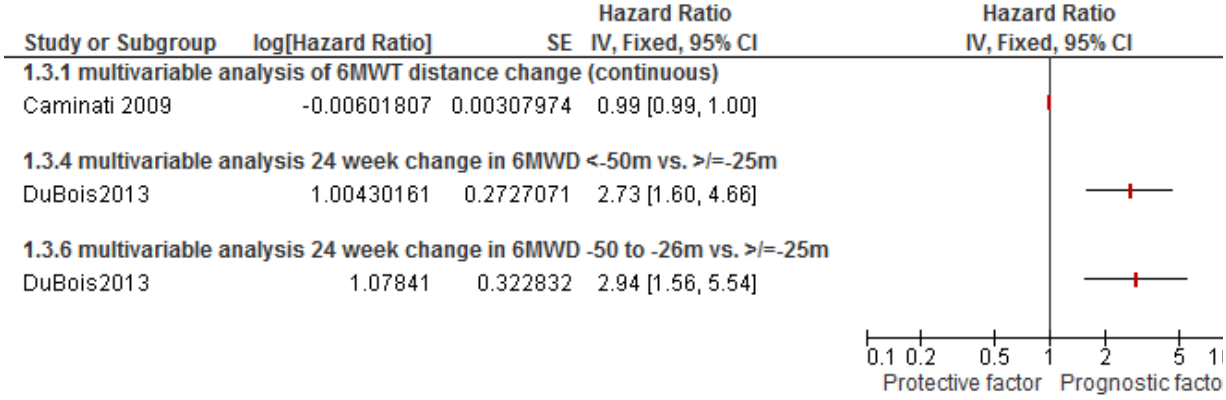
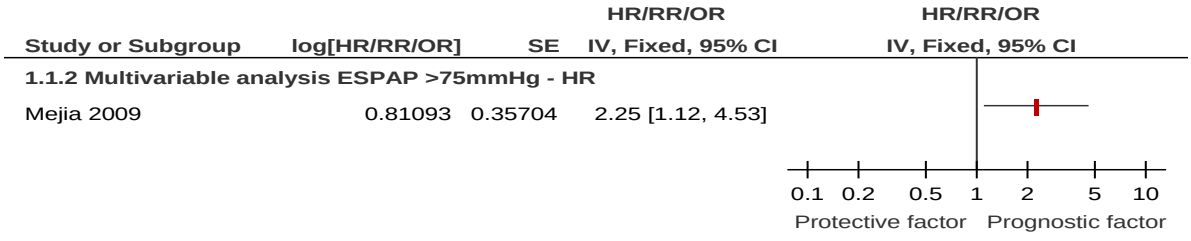


Figure 10: Serial change in 6MWD: mortality



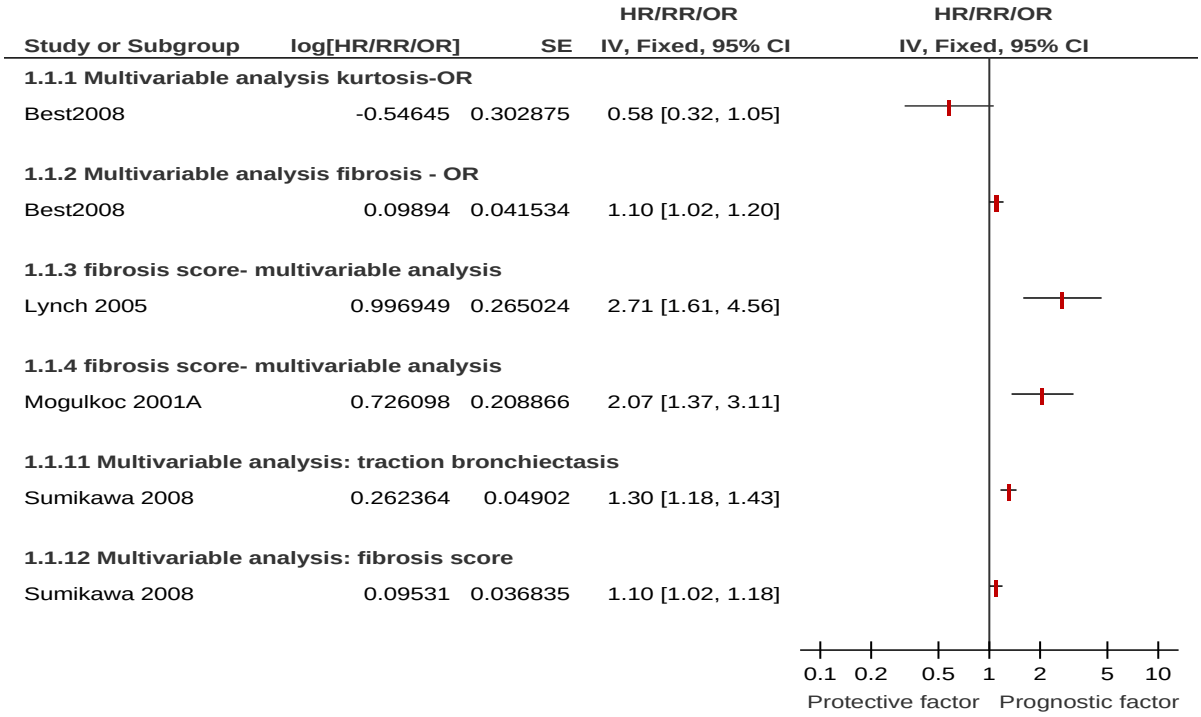
E.2.3 Echocardiography

Figure 11: Baseline pulmonary arterial pressure: mortality



E.2.4 HRCT scores

Figure 12: Baseline HRCT features: mortality



E.3 Pulmonary rehabilitation

Figure 13: Change in 6-minute walk distance (m) immediately following training in pulmonary rehabilitation vs. control in people with IPF

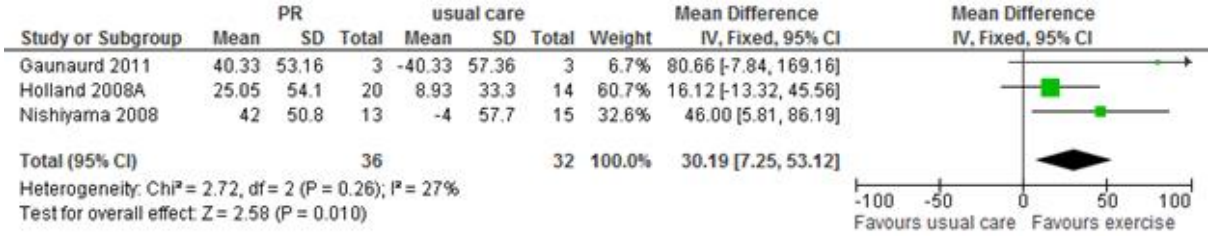


Figure 14: Change in 6-minute walk test distance (m) at long-term follow-up in pulmonary rehabilitation vs. control in people with IPF

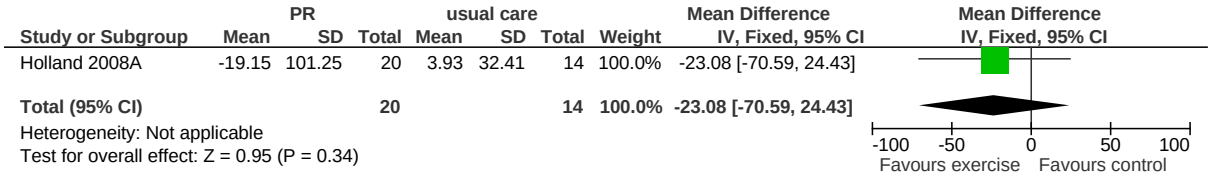


Figure 15: Change in dyspnoea score immediately following training in pulmonary rehabilitation vs. control in people with IPF

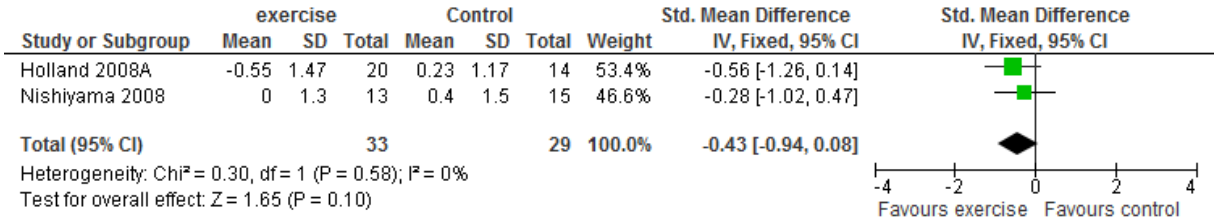


Figure 16: Change in dyspnoea score at long-term follow-up in pulmonary rehabilitation vs. control in people with IPF

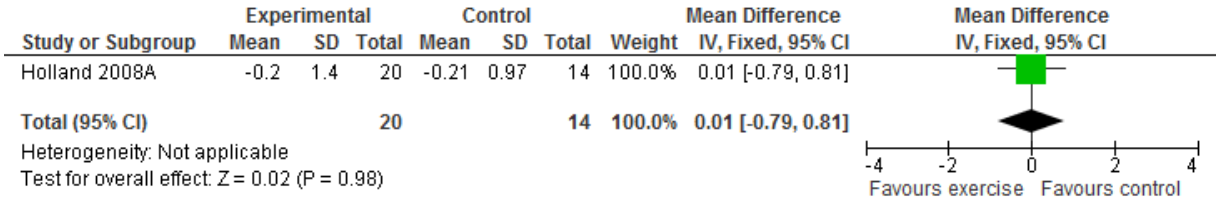


Figure 17: Change in quality of life immediately following training in pulmonary rehabilitation vs. control in people with IPF

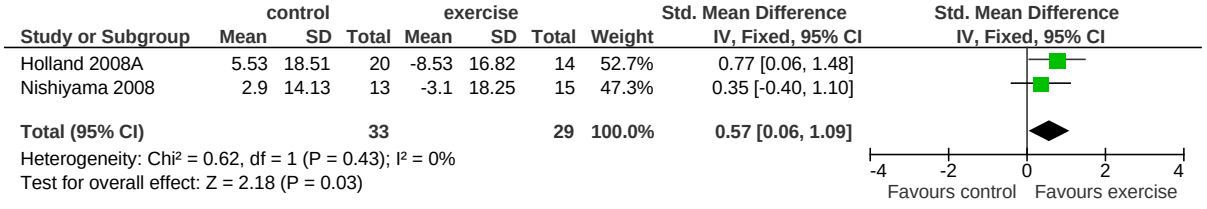


Figure 18: Change in quality of life at long-term follow-up in pulmonary rehabilitation vs. control

in people with IPF

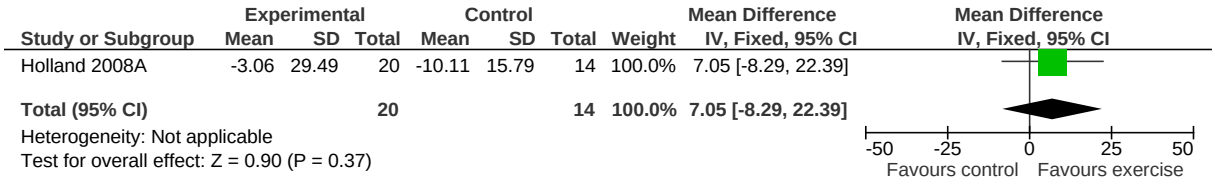


Figure 19: Six month survival in pulmonary rehabilitation vs. control in people with IPF

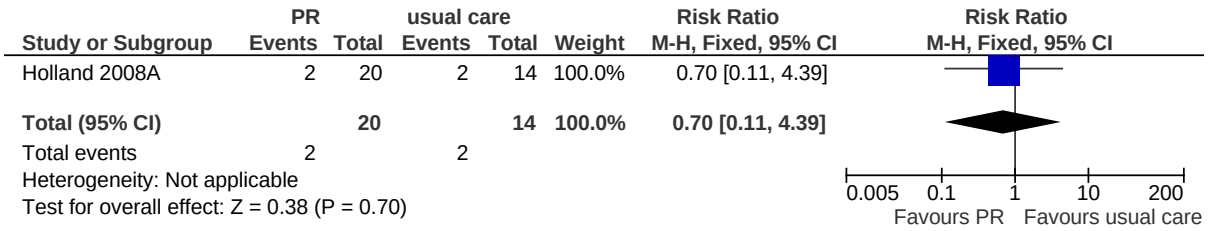


Figure 20: QoL: SF36 domain: physical functioning score immediately following training in pulmonary rehabilitation vs. usual care in people with IPF

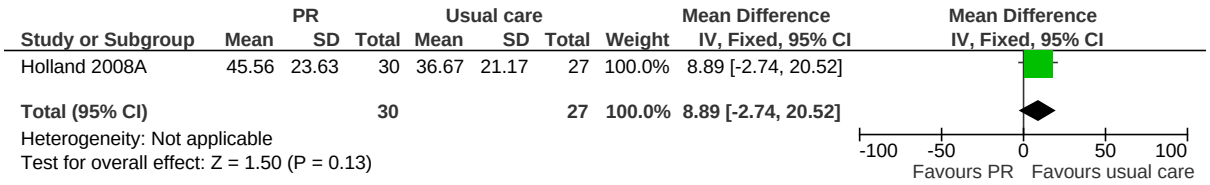


Figure 21: QoL: SF36 domain: physical role functioning score immediately following training in pulmonary rehabilitation vs. usual care in people with IPF

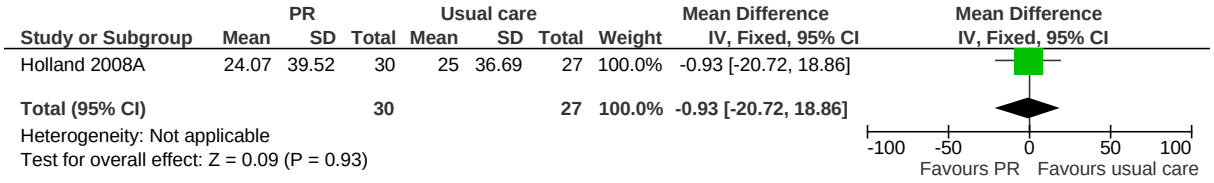


Figure 22: QoL: SF36 domain: vitality score immediately following training in pulmonary rehabilitation vs. usual care in people with IPF

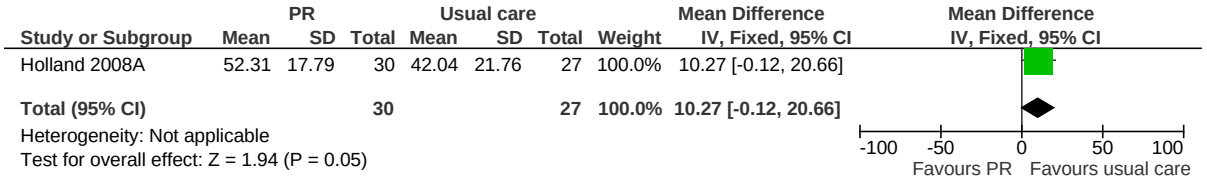


Figure 23: QoL: SF36 domain: bodily pain score immediately following training in pulmonary rehabilitation vs. usual care in people with IPF

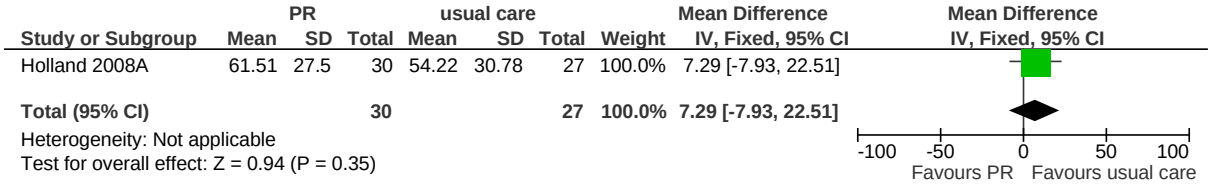


Figure 24: QoL: SF36 domain: general health perceptions score immediately following training in pulmonary rehabilitation vs. usual care in people with IPF

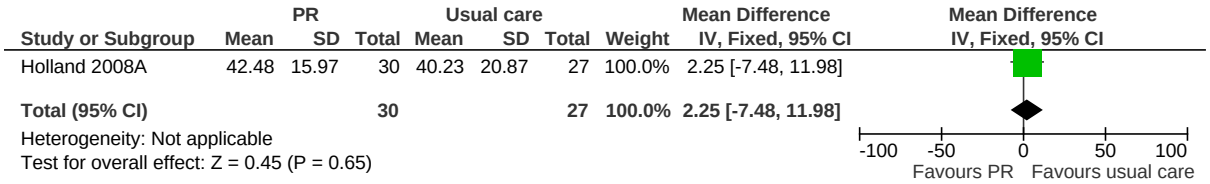


Figure 25: QoL: SF36 domain: social role functioning score immediately following training in pulmonary rehabilitation vs. usual care in people with IPF

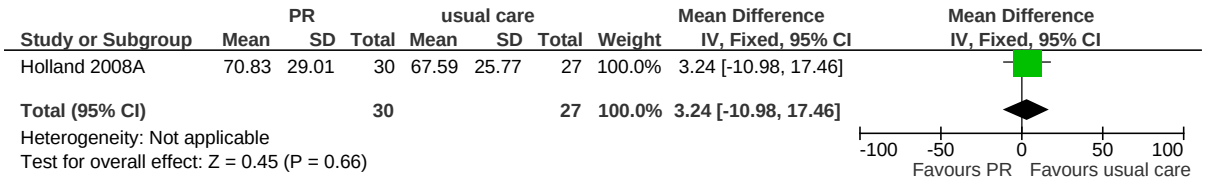


Figure 26: QoL: SF36 domain: emotional role functioning score immediately following training in pulmonary rehabilitation vs. usual care in people with IPF

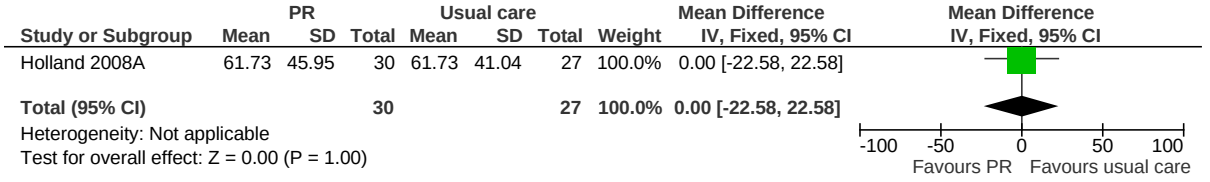


Figure 27: QoL: SF36 domain: mental health score immediately following training in pulmonary rehabilitation vs. usual care in people with IPF

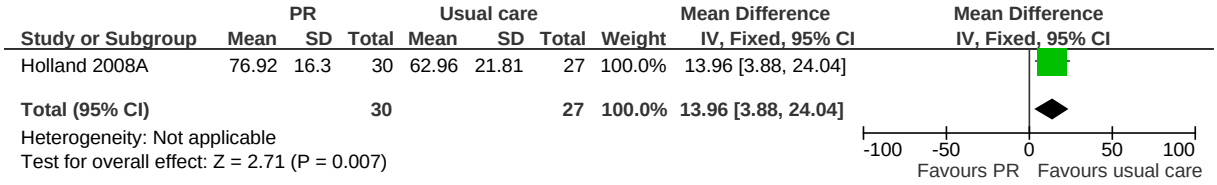
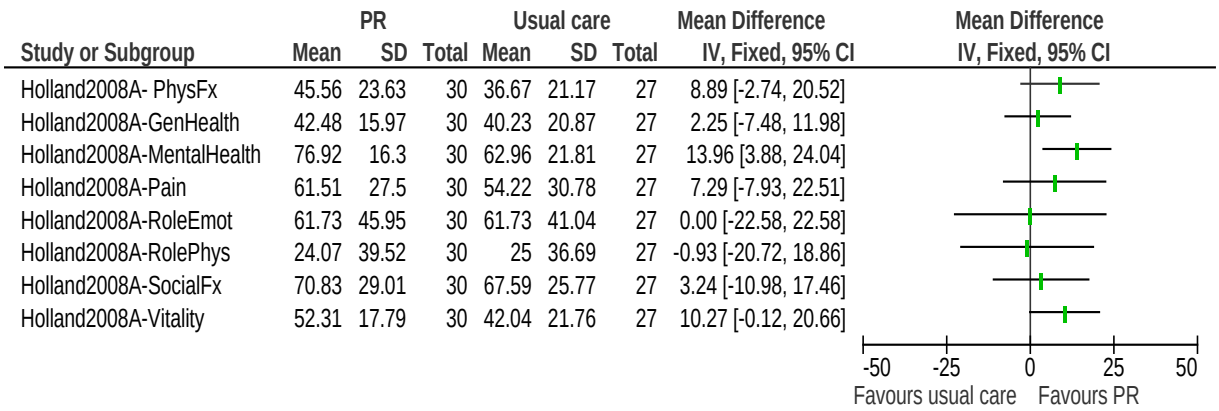


Figure 28: QoL: All SF36 domain scores immediately following training in pulmonary rehabilitation vs. usual care in people with IPF



E.4 Best supportive care

E.4.1 Oxygen management

Figure 29: Mortality (12 months) in patients receiving oxygen vs. air in people with IPF

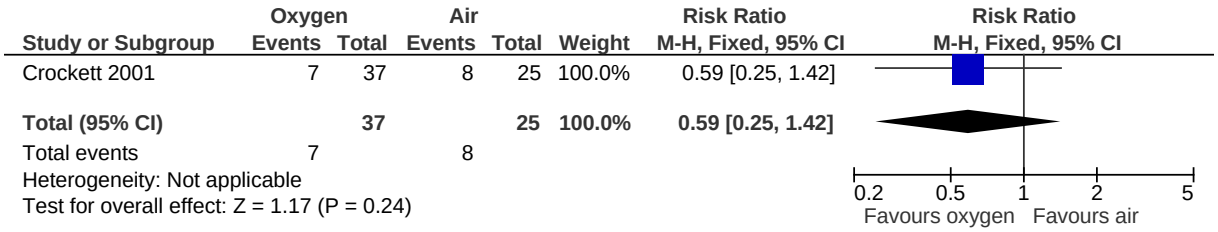


Figure 30: Mortality (24 months) in patients receiving oxygen vs. air in people with IPF

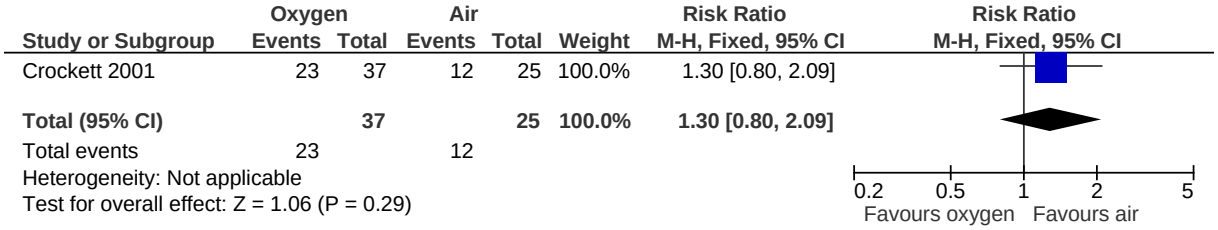


Figure 31: Mortality (3 years) in patients receiving oxygen vs. air in people with IPF

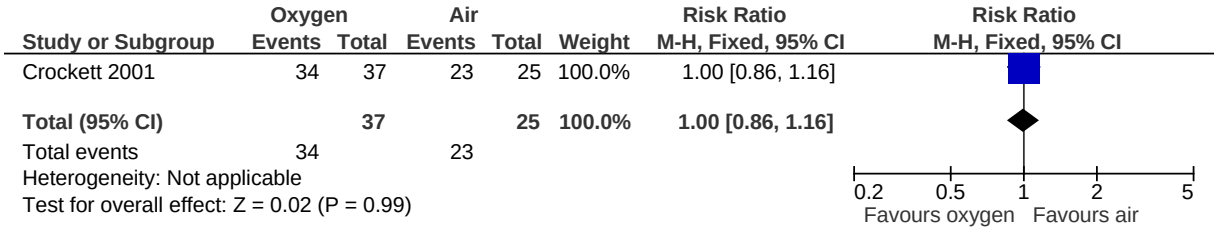


Figure 32: Arterial oxygen saturation in patients receiving oxygen vs. air in people with IPF immediately after treatment period

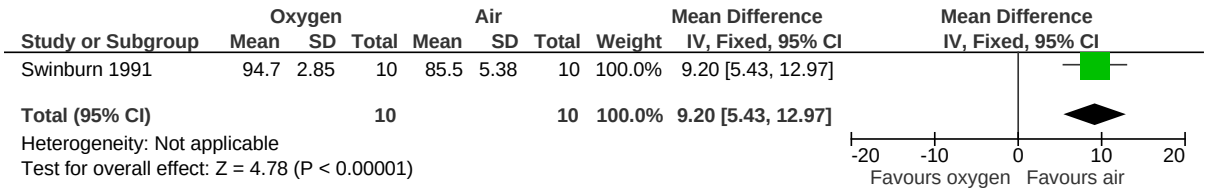
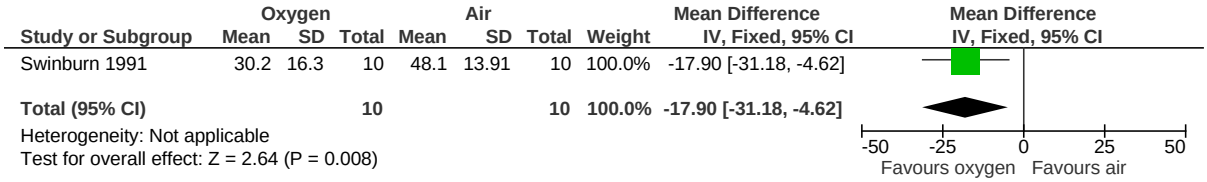


Figure 33: Dyspnoea (VAS) in patients receiving oxygen vs. air in people with IPF immediately after treatment period



E.4.2 Prednisolone for the palliation of cough

The data from these studies were not meta- analysable therefore forest plots for these outcomes could not be provided; see the clinical evidence profile and the evidence tables for further information.

E.4.3 Thalidomide for the palliation of cough

The data from these studies were not meta- analysable therefore forest plots for these outcomes could not be provide; see the clinical evidence profile and the evidence tables for further information.

E.4.4 Morphine for the palliation of breathlessness

The data from these studies were not meta- analysable therefore forest plots for these outcomes could not be provided; see the clinical evidence profile and the evidence tables for further information.

E.5 Pharmacological interventions

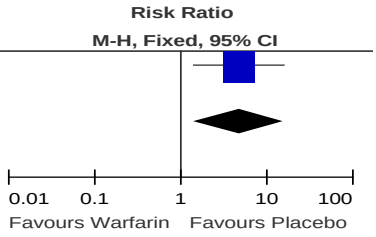
(See Appendix I for calculations of standard errors from hazard ratios, risk ratios and odds ratios)

E.5.1 Warfarin vs. Placebo

Figure 34: All-cause mortality

Study or Subgroup	Warfarin Events	Warfarin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Noth 2012	14	72	3	73	100.0%	4.73 [1.42, 15.77]
Total (95% CI)		**72**		**73**	**100.0%**	**4.73 [1.42, 15.77]**
Total events	14		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.53 (P = 0.01)

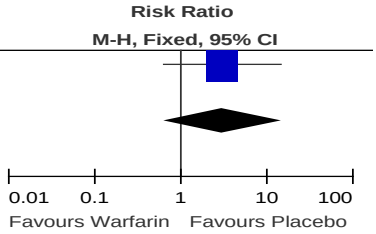


Source: ***At trial stop***

Figure 35: Hospitalisations due to IPF complications (including IPF exacerbations)

Study or Subgroup	Warfarin Events	Warfarin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Noth 2012	6	72	2	73	100.0%	3.04 [0.63, 14.57]
Total (95% CI)		**72**		**73**	**100.0%**	**3.04 [0.63, 14.57]**
Total events	6		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.16)

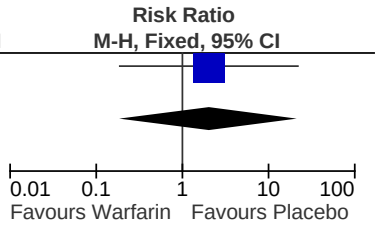


Source: ***At trial stop***

Figure 36: Adverse event: Major bleeding

Study or Subgroup	Warfarin Events	Warfarin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Noth 2012	2	72	1	73	100.0%	2.03 [0.19, 21.87]
Total (95% CI)		**72**		**73**	**100.0%**	**2.03 [0.19, 21.87]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

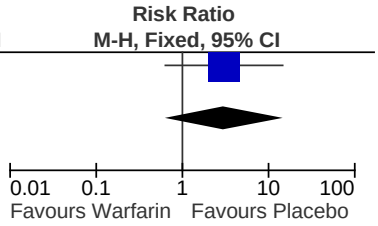


Source: ***At trial stop***

Figure 37: Adverse event: minor bleeding

Study or Subgroup	Warfarin Events	Warfarin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Noth 2012	6	72	2	73	100.0%	3.04 [0.63, 14.57]
Total (95% CI)		**72**		**73**	**100.0%**	**3.04 [0.63, 14.57]**
Total events	6		2			

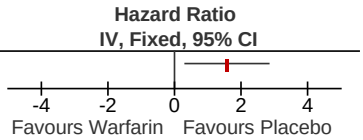
Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.16)



Source: ***At trial stop***

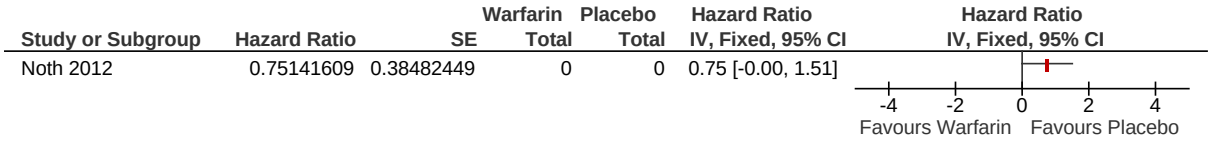
Figure 38: All-cause mortality (HR)

Study or Subgroup	Hazard Ratio	SE	Warfarin Total	Placebo Total	Hazard Ratio IV, Fixed, 95% CI
Noth 2012	1.5789787	0.64044424	0	0	1.58 [0.32, 2.83]



Source: extrapolated data

Figure 39: All-cause mortality or non-elective non bleeding hospitalisations (HR)



E.5.2 Warfarin & prednisolone vs. Prednisolone

Figure 40: Hospitalisations due to IPF complications (including exacerbations)

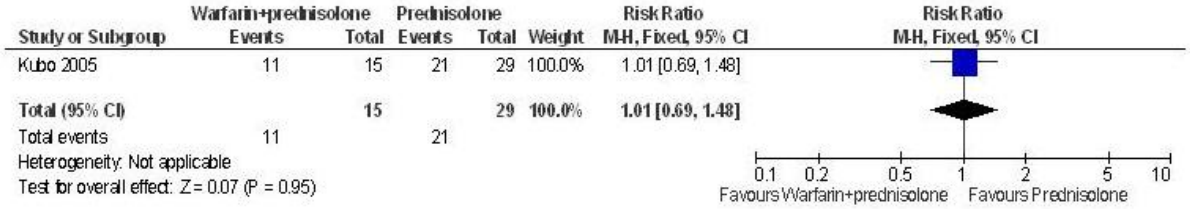


Figure 41: Mortality

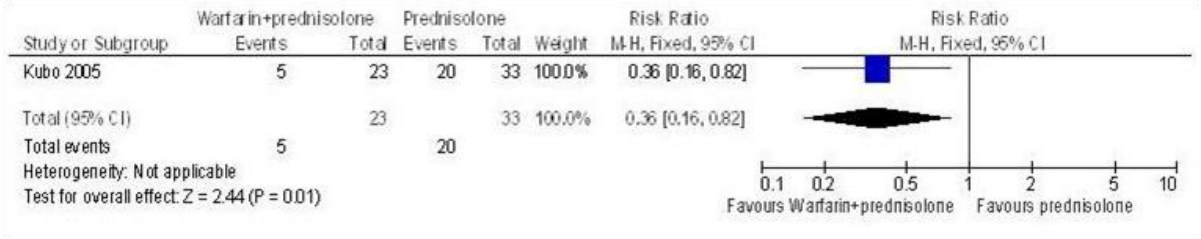


Figure 42: 1 year survival

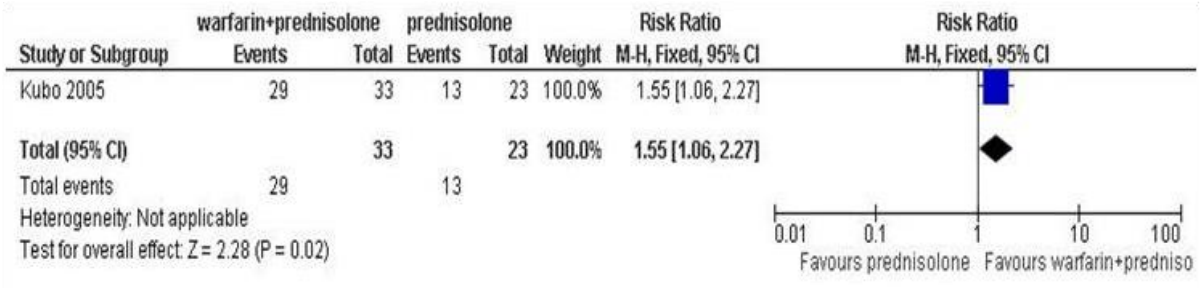
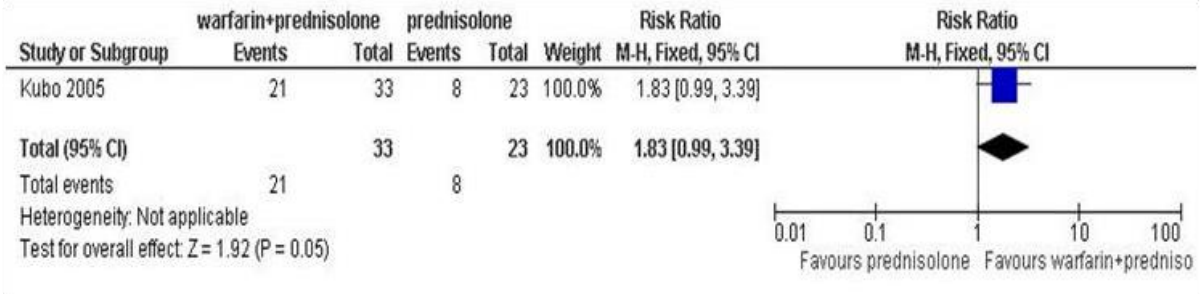


Figure 43: 3 year survival



E.5.3 Sildenafil vs. Placebo

Figure 44: Lung capacity (FVC)

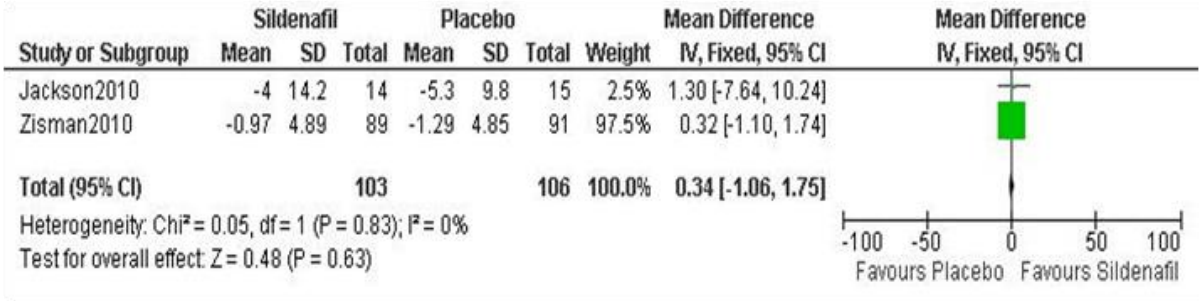


Figure 45: Gas transfer (DLCO)

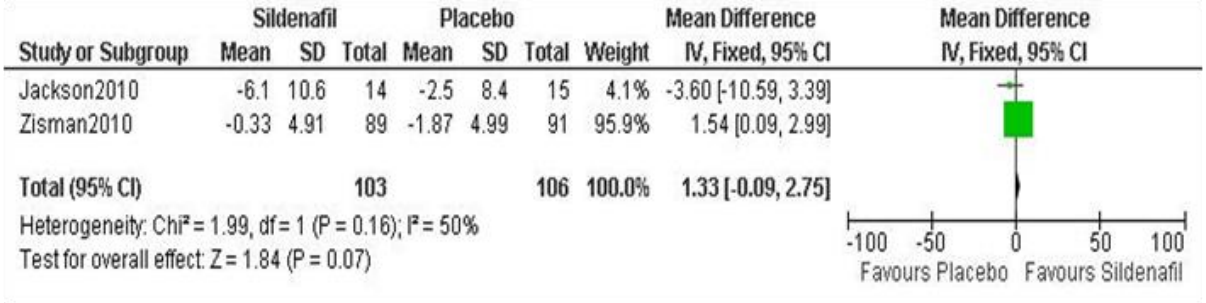


Figure 46: Performance on 6MWT (distance walked)

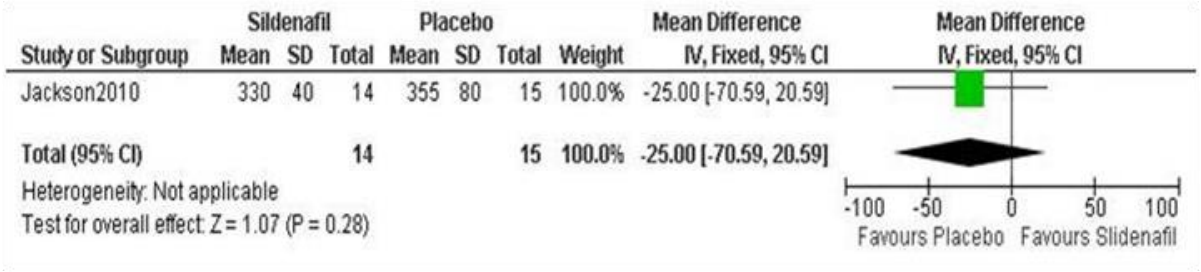


Figure 47: Mortality

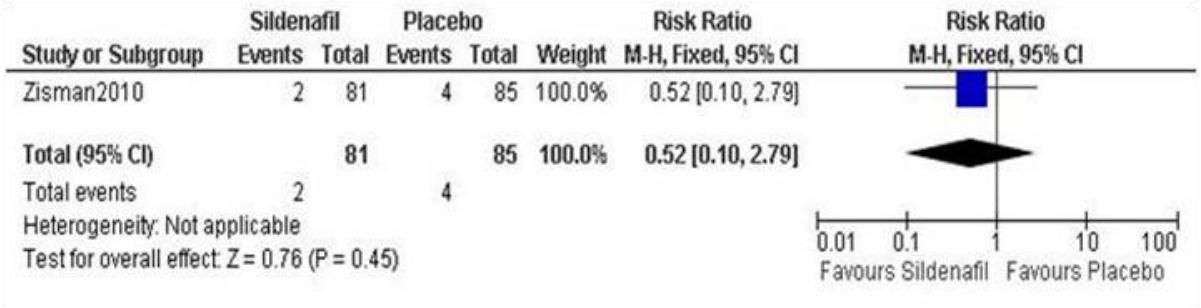


Figure 48: Adverse events: chest pain/coronary artery disease

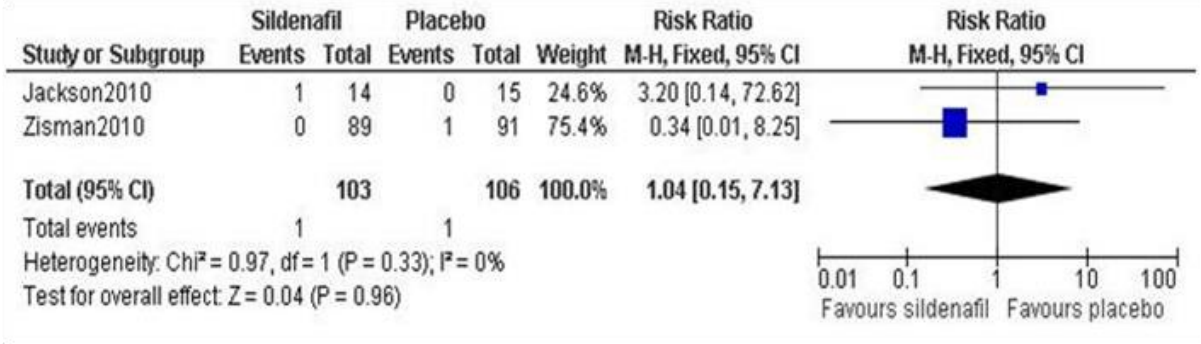


Figure 49: Adverse events: facial flushing

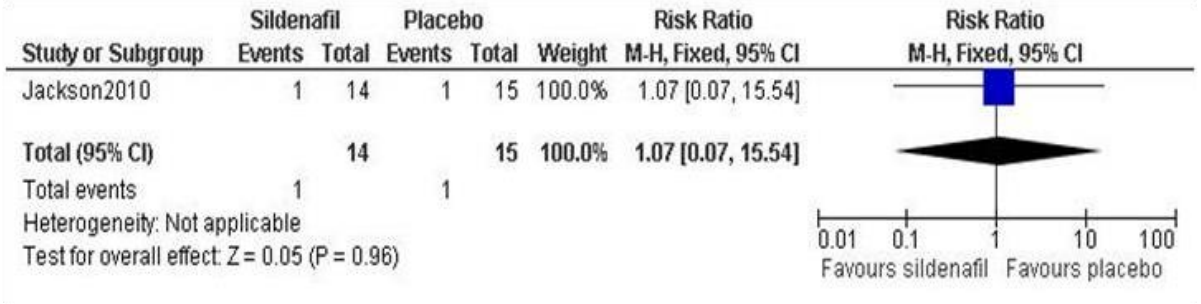


Figure 50: Adverse events: visual disturbance

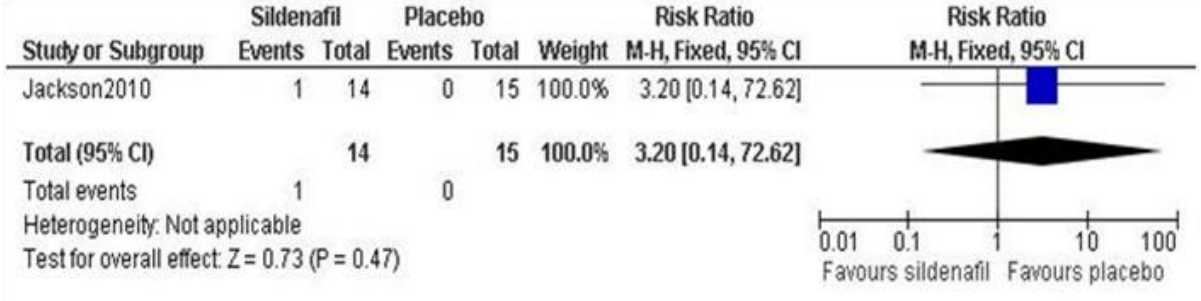


Figure 51: Dyspnoea (Borg)

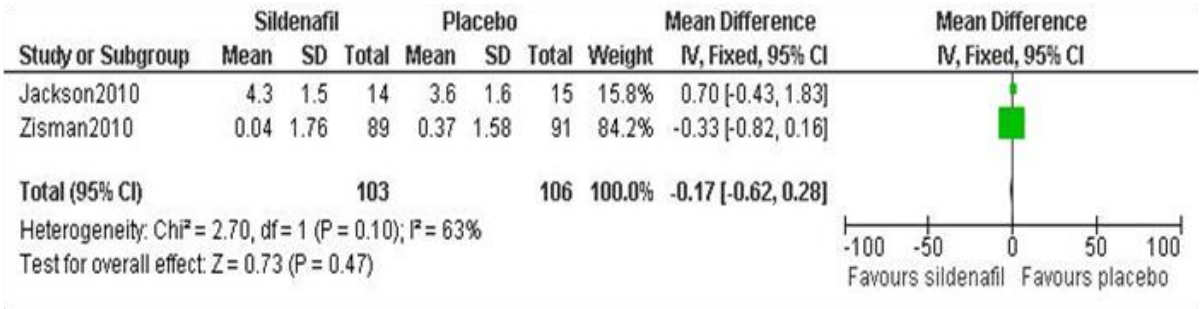
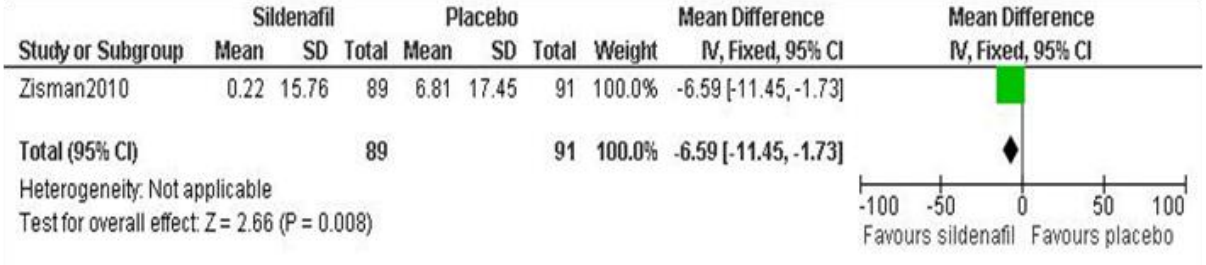


Figure 52: Dyspnoea (shortness of breath questionnaire)



E.5.4 Bosentan vs. Placebo

Figure 53: 6MWT (distance walked)

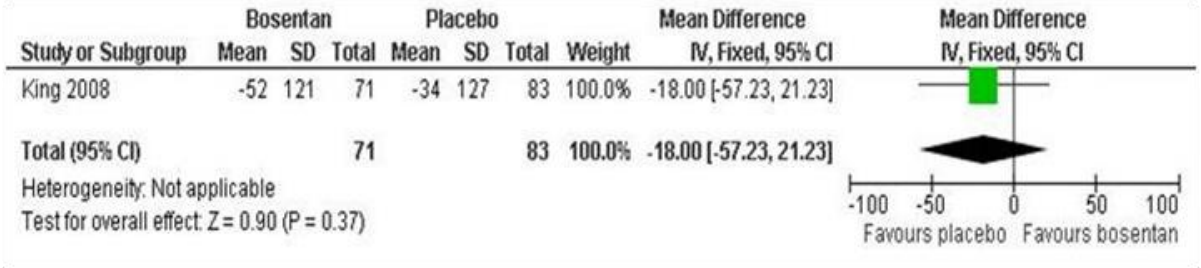


Figure 54: Mortality

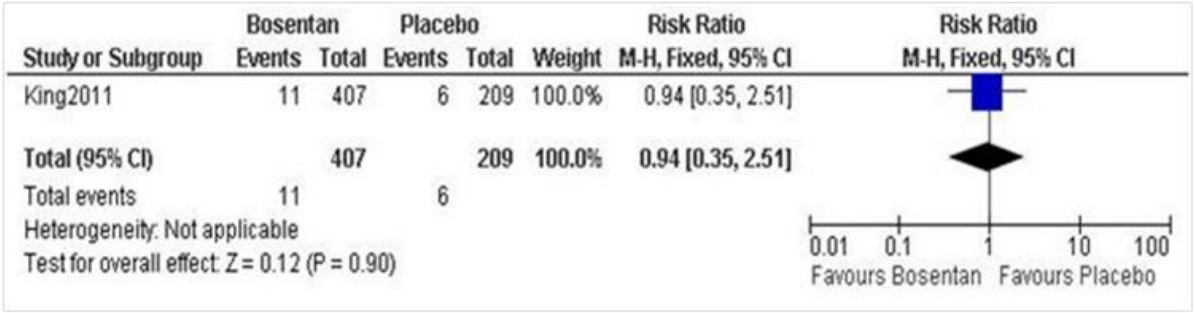


Figure 55: Adverse events (abnormal LFTs)

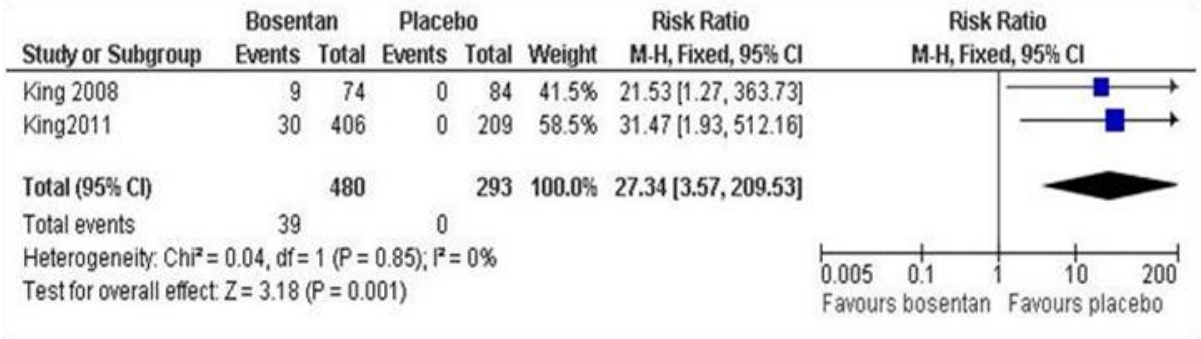


Figure 56: Adverse events (drug hypersensitivity)

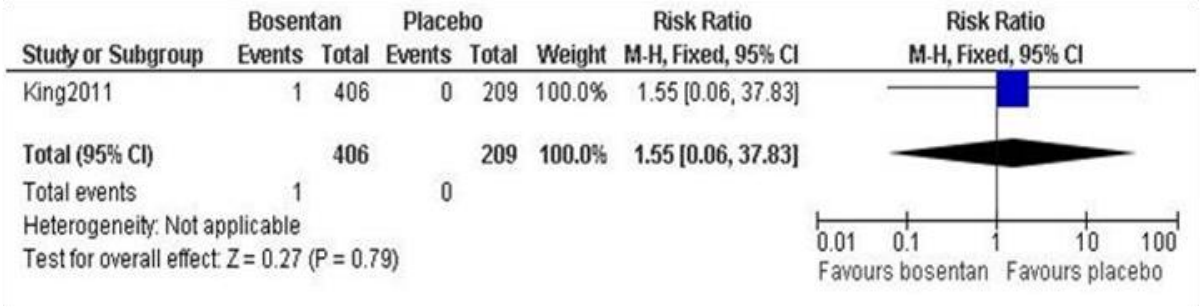


Figure 57: Dyspnoea

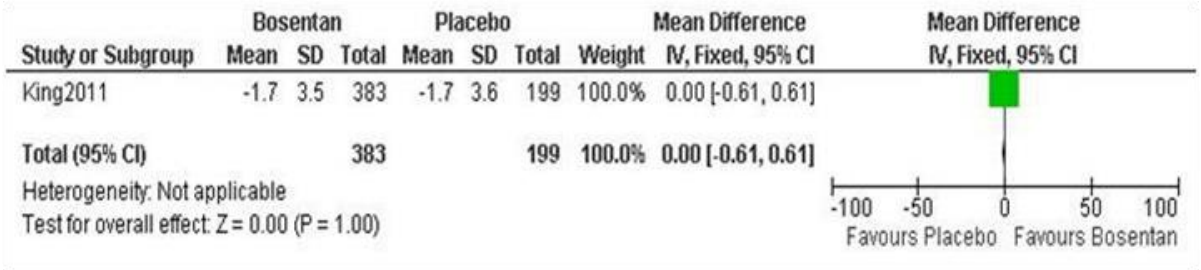
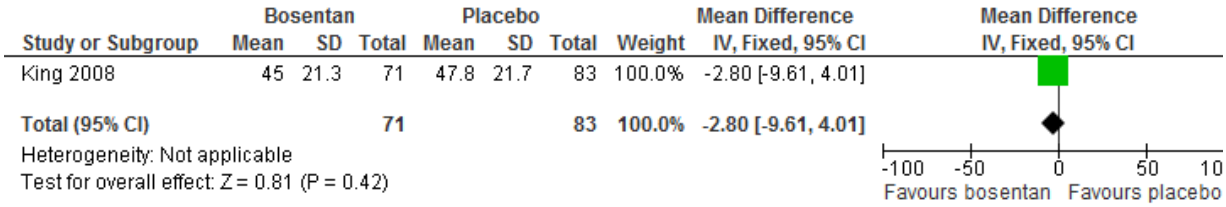


Figure 58: QOL: Total SGRQ at 6 months follow up



E.5.5 N-acetylcysteine vs. Placebo

Figure 59: Lung capacity (FVC)

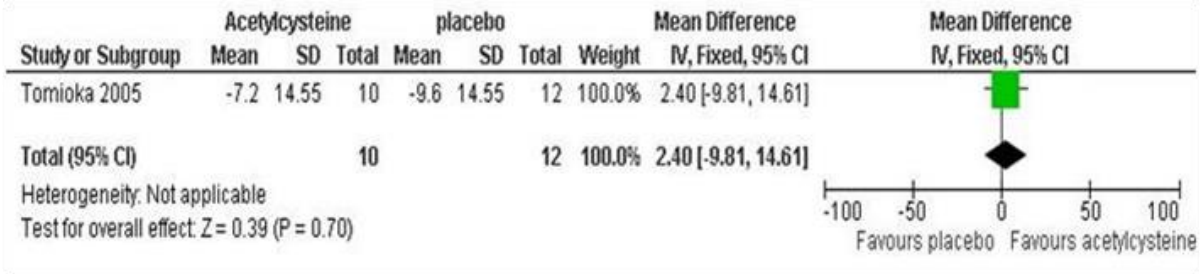


Figure 60: Gas transfer (DLCO)

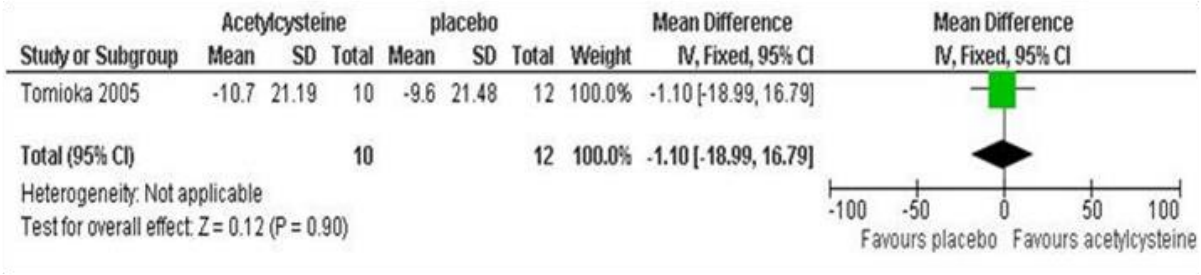


Figure 61: Performance on 6MWT (distance walked)

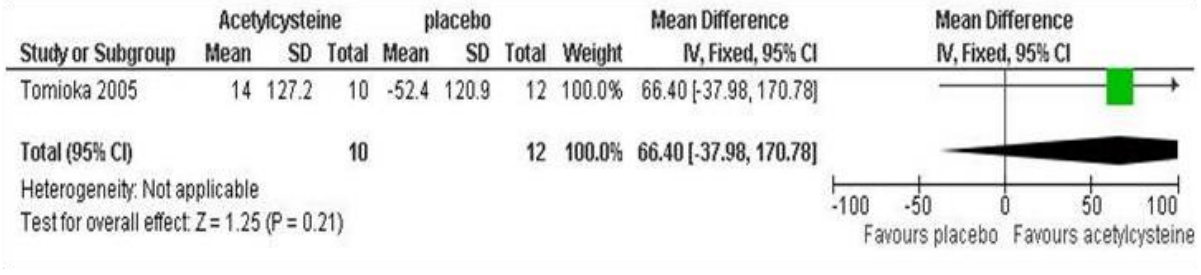


Figure 62: Performance on 6MWT (lowest SaO2)

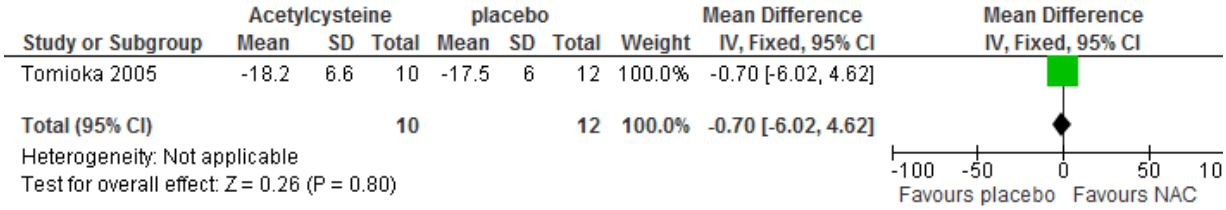


Figure 63: QOL: SF36: Physical function

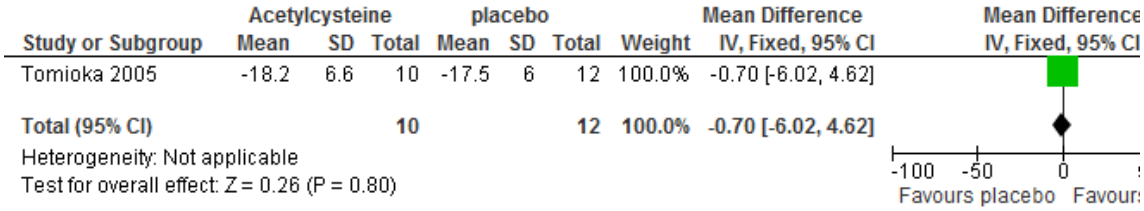


Figure 64: QOL: SF36: Physical role functioning

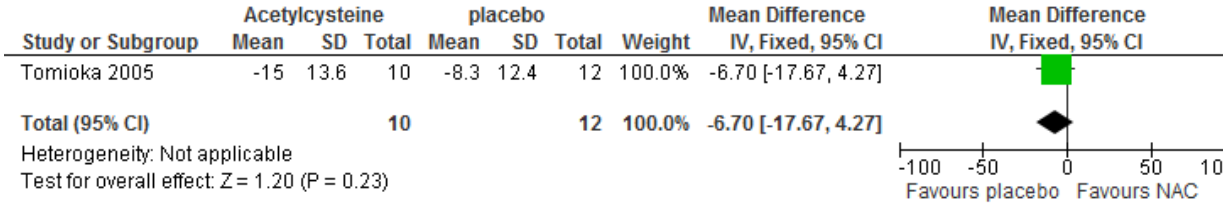


Figure 65: QOL: SF36: Vitality

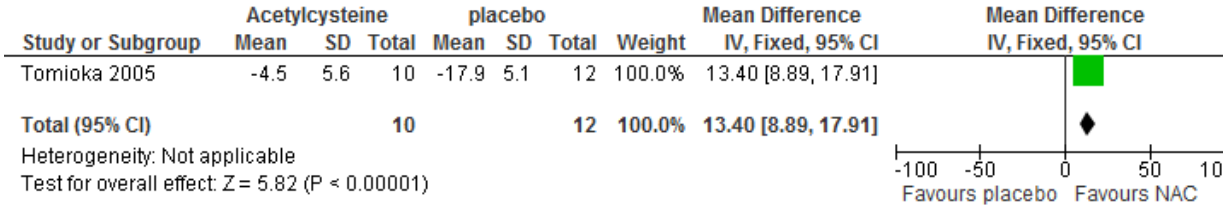


Figure 66: QOL: SF36: Bodily pain

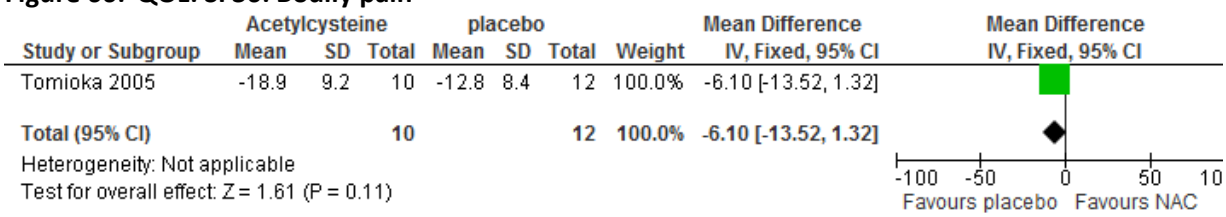


Figure 67: QOL: SF36: general health perceptions

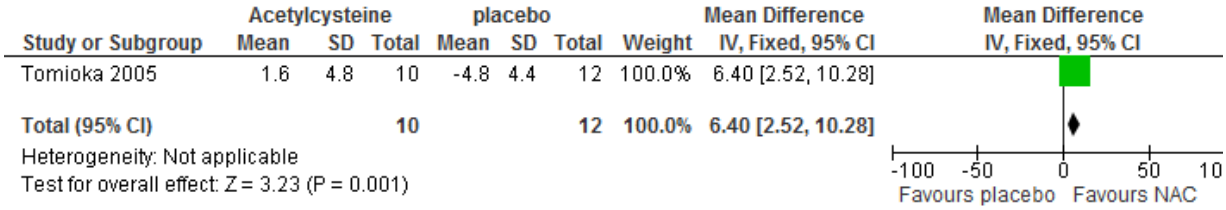


Figure 68: QOL: SF36: Social role functioning

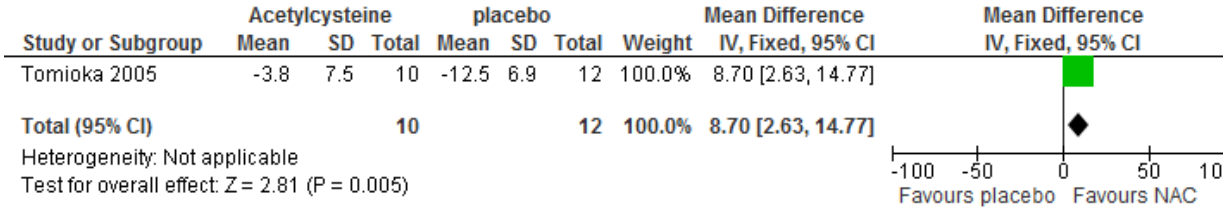


Figure 69: QOL: SF36: emotional role functioning

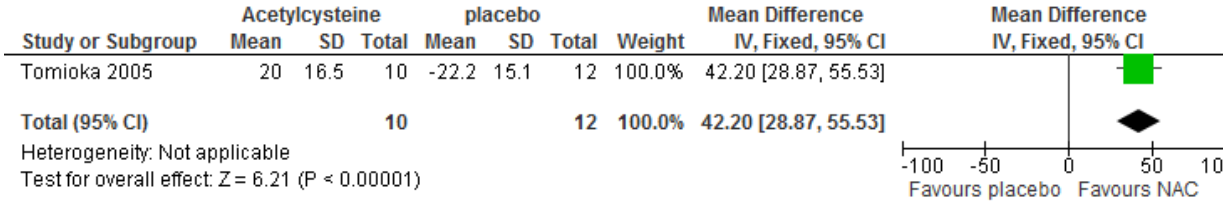
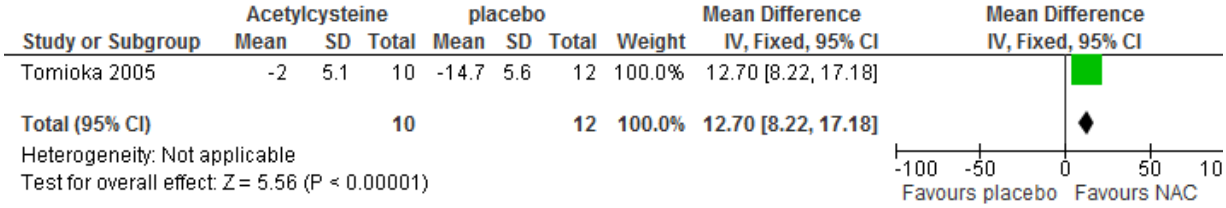


Figure 70: QOL: SF36: Mental health



E.5.6 N-acetylcysteine vs. no treatment

Figure 71: Lung capacity (FVC)

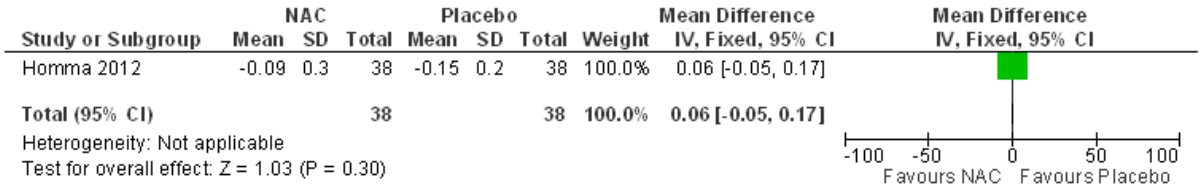
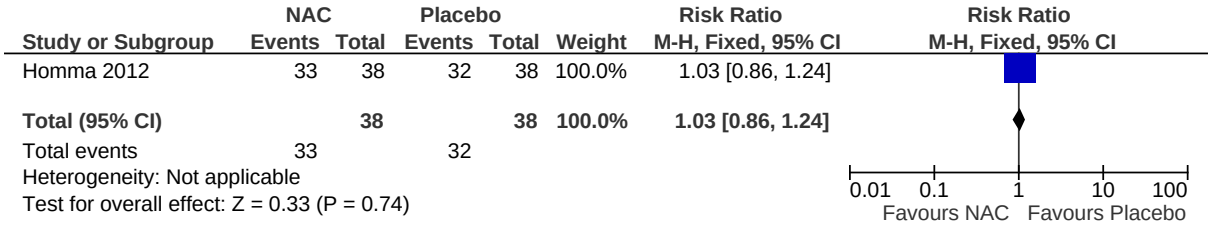


Figure 72: Hospitalisations due to IPF complications (including IPF exacerbations)

Figure 73: Dyspnoea



E.5.7 Co-trimoxazole vs. Placebo

Figure 74: Mortality (ITT)

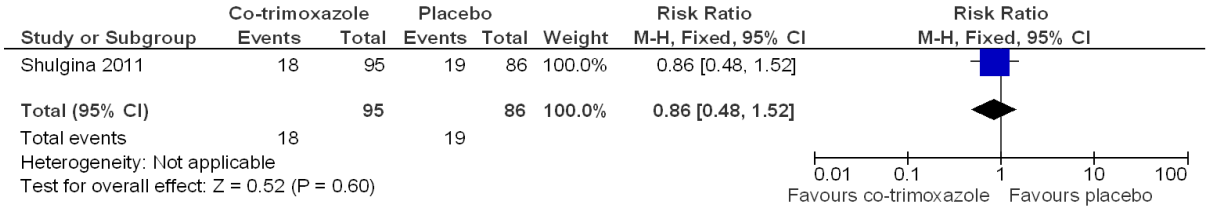


Figure 75: Mortality (per-protocol)

Figure 76: Lung capacity: FVC (ml)

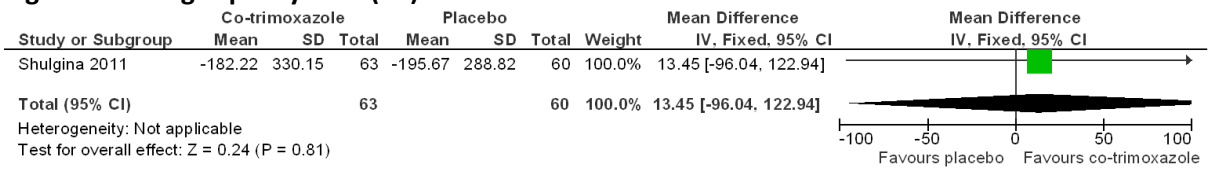


Figure 77: Lung capacity: FVC (% predicted)

Study or Subgroup	Co-trimoxazole Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Shulgina 2011	-4.65	9.96	63	-4.79	8.7	60	100.0%	0.14 [-3.16, 3.44]
Total (95% CI)			**63**			**60**	**100.0%**	**0.14 [-3.16, 3.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.93)

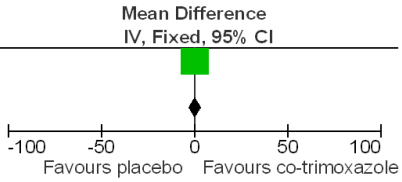


Figure 78: Gas transfer: DLCO (mmol/min/KPa)

Study or Subgroup	Co-trimoxazole Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Shulgina 2011	-0.3	0.68	45	-0.22	0.81	50	100.0%	-0.08 [-0.38, 0.22]
Total (95% CI)			**45**			**50**	**100.0%**	**-0.08 [-0.38, 0.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)

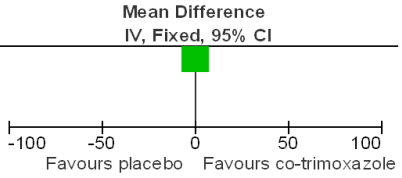


Figure 79: Gas transfer: DLCO % predicted

Study or Subgroup	Co-trimoxazole Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Shulgina 2011	-3.67	8.1	45	-3.88	10.75	50	100.0%	0.21 [-3.60, 4.02]
Total (95% CI)			**45**			**50**	**100.0%**	**0.21 [-3.60, 4.02]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)

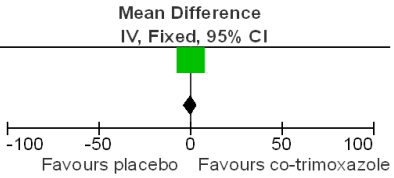


Figure 80: Health related quality of life: SGRQ total (units)

Study or Subgroup	Co-trimoxazole Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Shulgina 2011	0.71	13.96	49	1.78	11.59	52	100.0%	-1.07 [-6.09, 3.95]
Total (95% CI)			**49**			**52**	**100.0%**	**-1.07 [-6.09, 3.95]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)

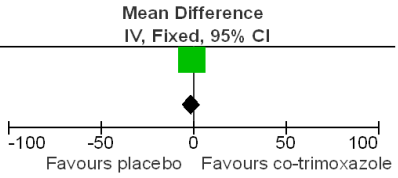


Figure 81: Performance on sub-maximal walk test: 6MWT (distance walked)

Study or Subgroup	Co-trimoxazole Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Shulgina 2011	-18.7	75.39	20	-19.48	86.49	31	100.0%	0.78 [-44.15, 45.71]
Total (95% CI)			**20**			**31**	**100.0%**	**0.78 [-44.15, 45.71]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)

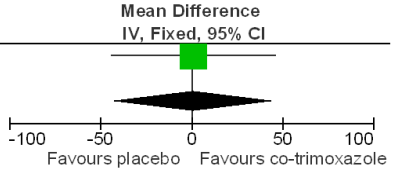


Figure 82: Performance on sub-maximal walk test: 6MWT (desaturation of 4% or more)

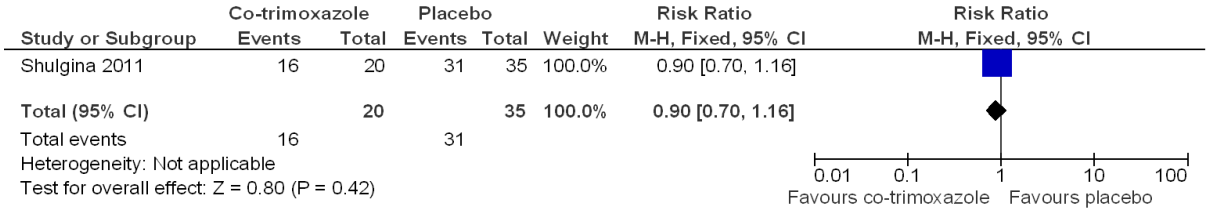
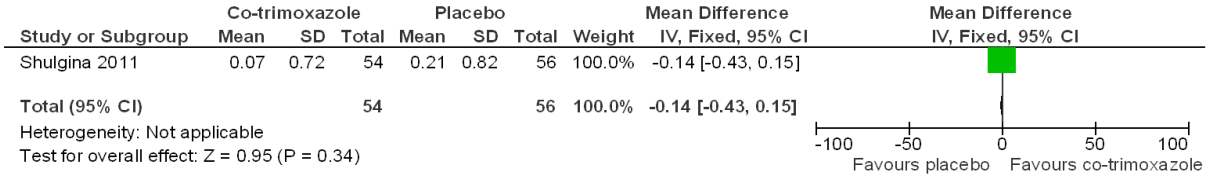


Figure 83: Dyspnoea: MRC score (units)



E.5.8 Ambrisentan vs. Placebo

Figure 84: Mortality

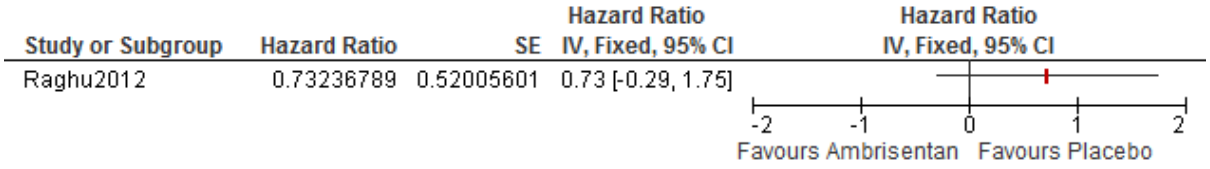
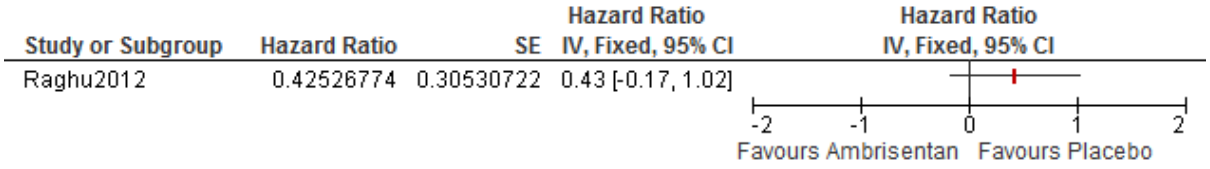


Figure 85: Decrease in lung function



E.5.9 Combination: Prednisolone & azathioprine vs. Prednisolone & placebo

Figure 86: Lung capacity (FVC)

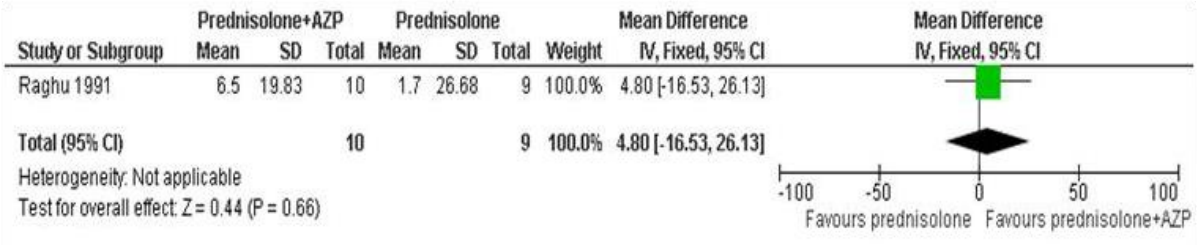


Figure 87: Gas transfer (DLCO)

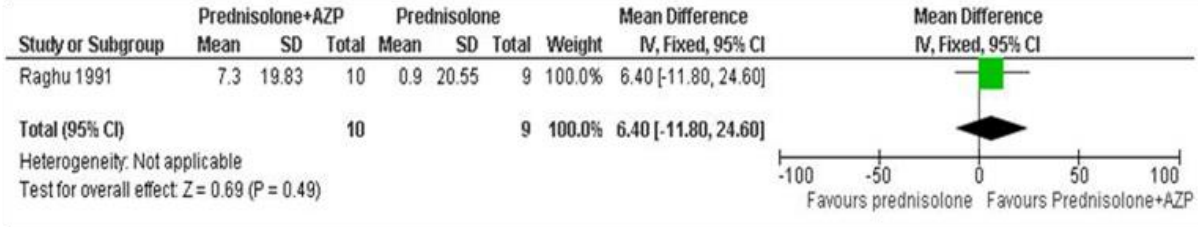


Figure 88: Mortality

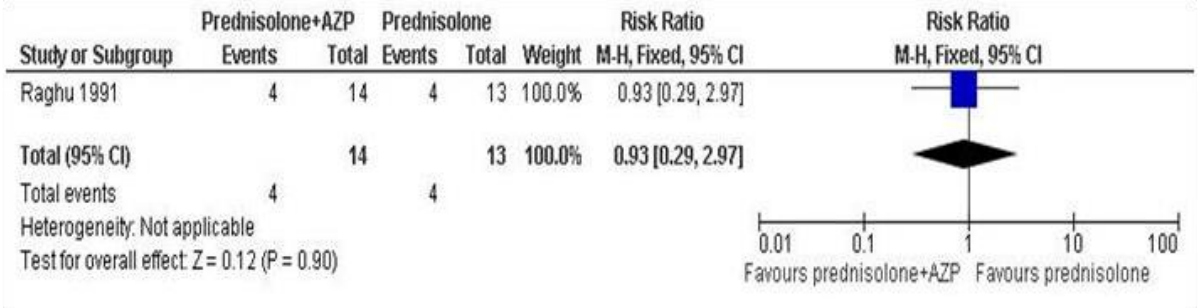


Figure 89: Adverse events: elevated liver enzymes

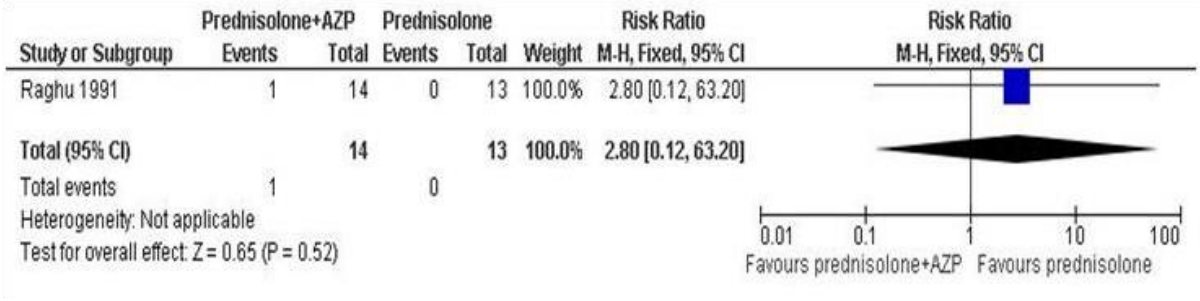
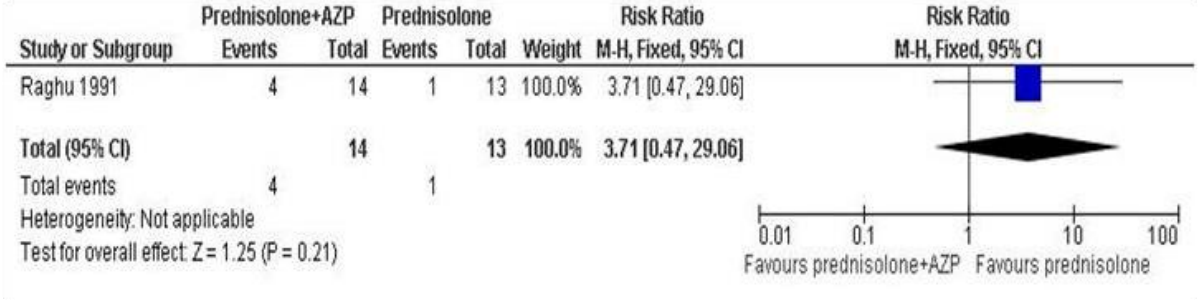


Figure 90: Adverse events: infections



E.5.10 Combination: Prednisolone & azathioprine & n-acetylcysteine vs. Azathioprine & prednisolone

Figure 91: lung capacity (FVC)- Available case analysis

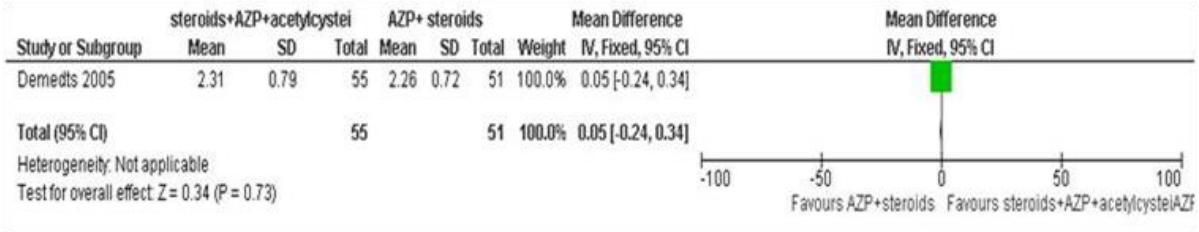


Figure 92: lung capacity (FVC)- Intention to treat analysis

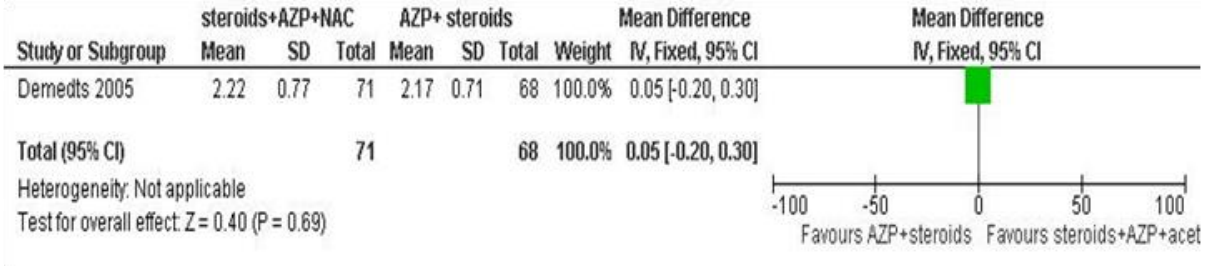


Figure 93: gas transfer (DLCO)- Available case analysis

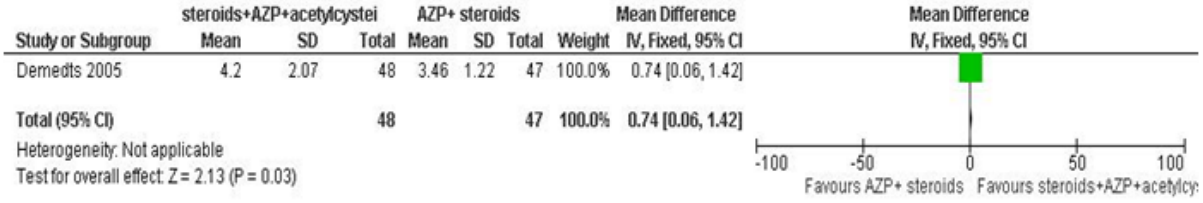


Figure 94: DLCO- Intention to treat analysis

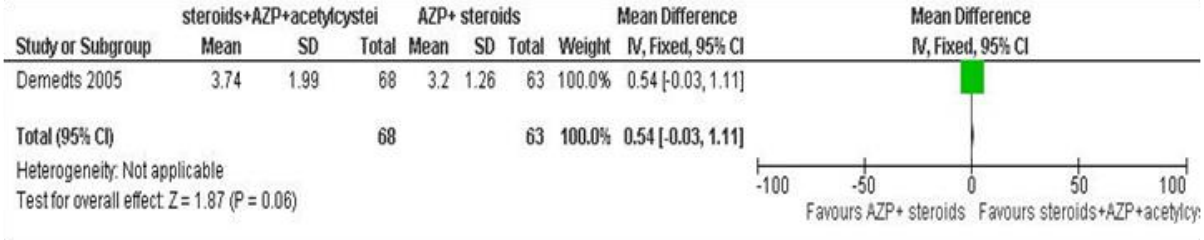


Figure 95: Mortality (all cause)

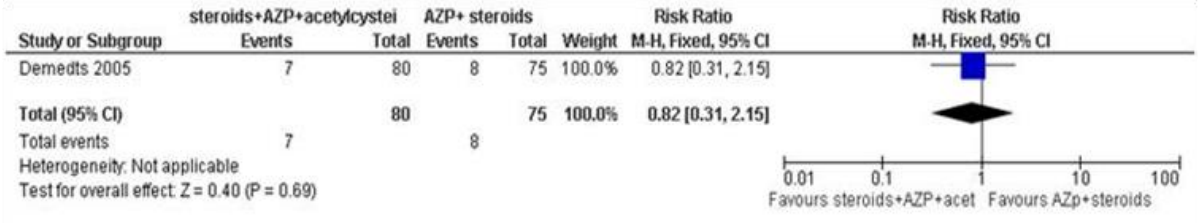
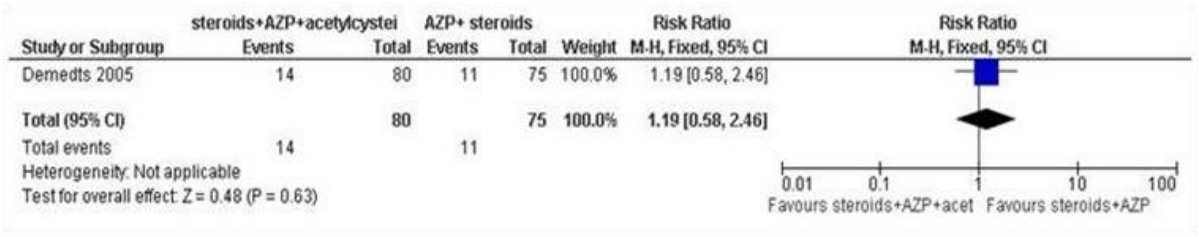
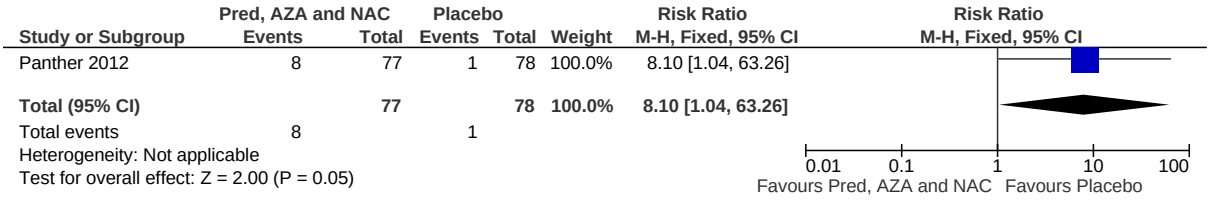


Figure 96: Adverse events: abnormal liver function tests



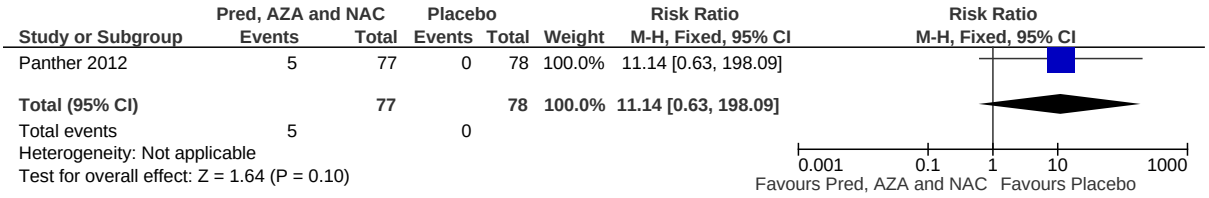
E.5.11 Combination: Prednisolone & azathioprine & n-acetylcysteine vs. Placebo

Figure 97: All-cause mortality at trial stop



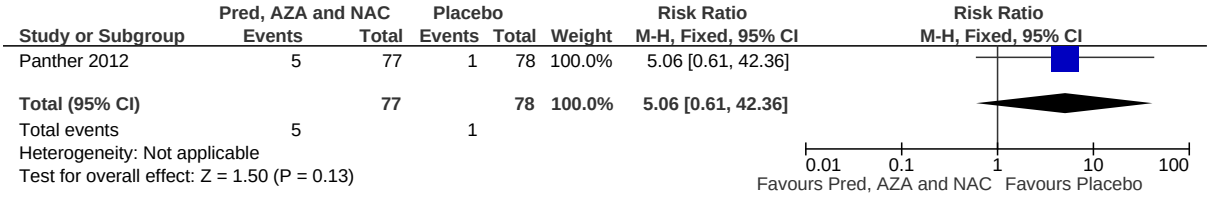
Source: At trial stop

Figure 98: Hospitalisations due to IPF exacerbations



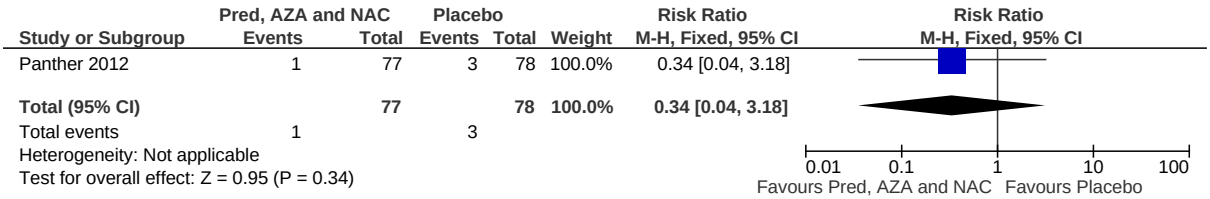
Source: At trial stop

Figure 99: Adverse events (infections)



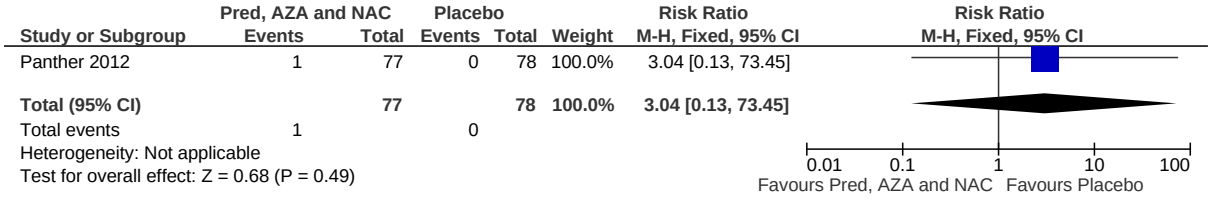
Source: At trial stop

Figure 100: Adverse events (GI)



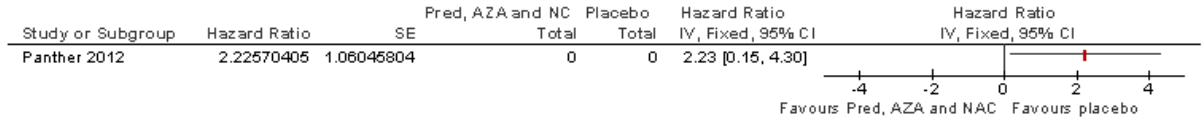
Source: At trial stop

Figure 101: Adverse events (metabolic)



Source: At trial stop

Figure 102: All-cause mortality



Source: Extrapolated data

E.6 Lung transplantation

E.6.1 Lung allocation score

Figure 103: Occurrence of transplantation in IPF patients transplanted before LAS was implemented vs. patients who were transplanted after LAS was implemented

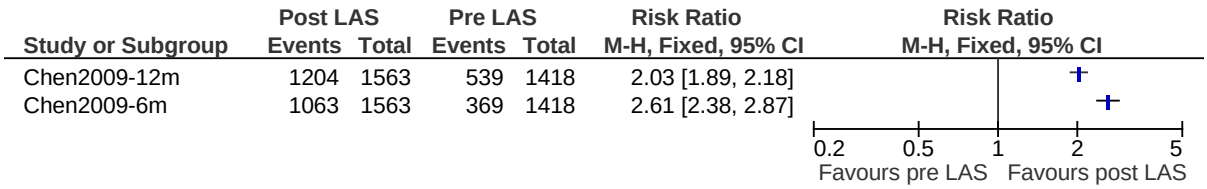


Figure 104: Post transplant mortality in IPF patients transplanted before LAS was implemented vs. patients who were transplanted after LAS was implemented

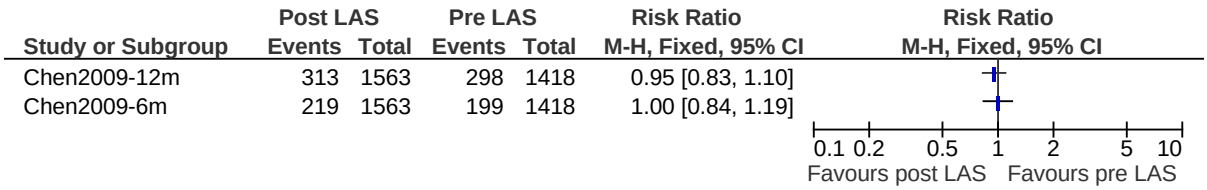


Figure 105: Waiting list mortality in IPF patients transplanted before LAS was implemented vs. patients who were transplanted after LAS was implemented

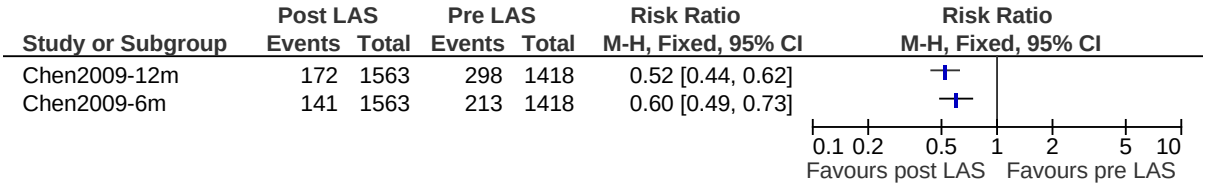


Figure 106: 1 year survival in IPF patients transplanted before LAS was implemented vs. patients who were transplanted after LAS was implemented

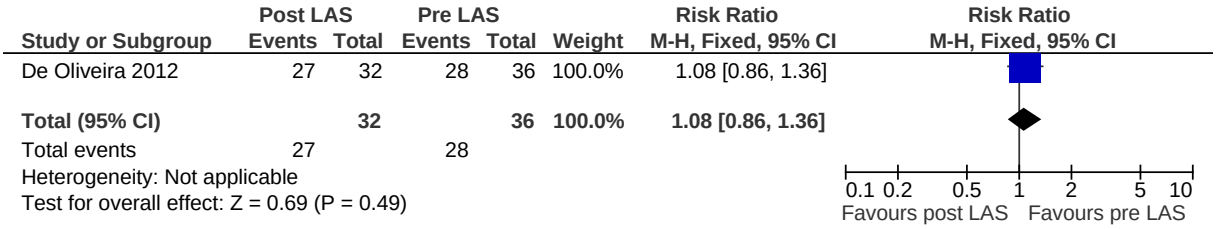


Figure 107: 3 year survival in IPF patients transplanted before LAS was implemented vs. patients who were transplanted after LAS was implemented

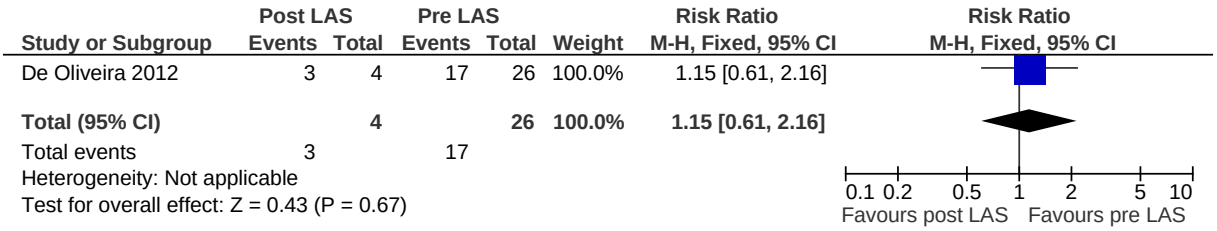


Figure 108: Readmission <30 days in IPF patients transplanted before LAS was implemented vs. patients who were transplanted after LAS was implemented

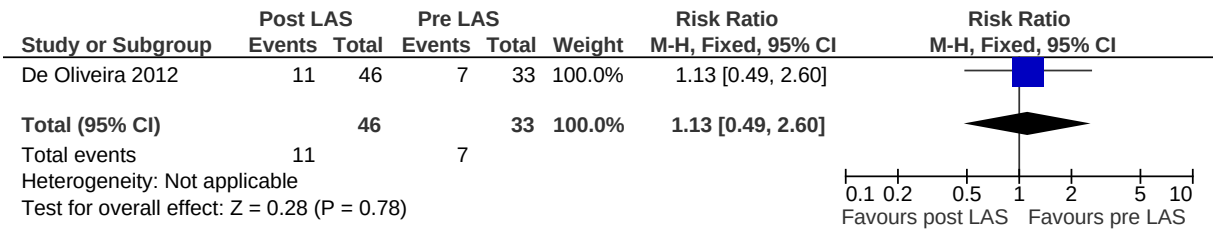
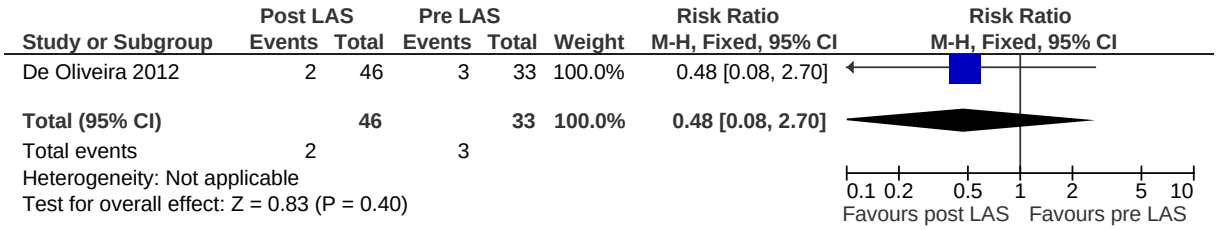


Figure 109: Hospital mortality in IPF patients transplanted before LAS was implemented vs. patients who were transplanted after LAS was implemented



E.7 Ventilation

Figure 110: In hospital mortality of patients with IPF on invasive mechanical ventilation vs. non-invasive mechanical ventilation

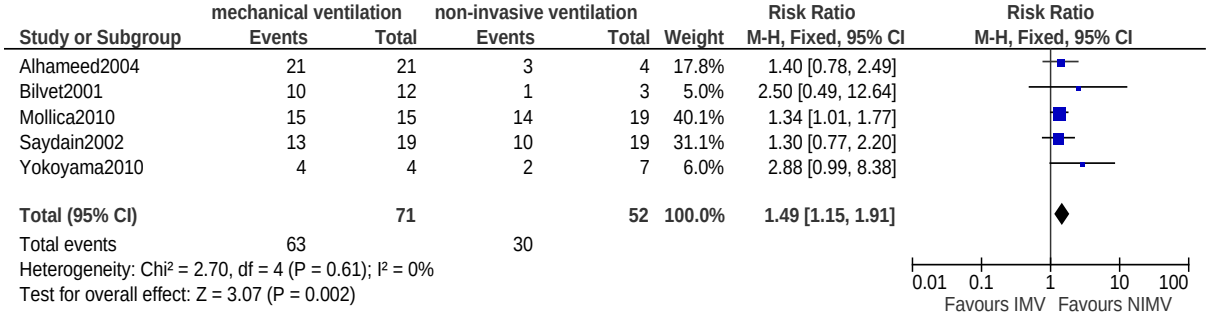


Figure 111: In hospital mortality of patients with IPF on Ventilation (invasive and non-invasive) vs. no ventilation

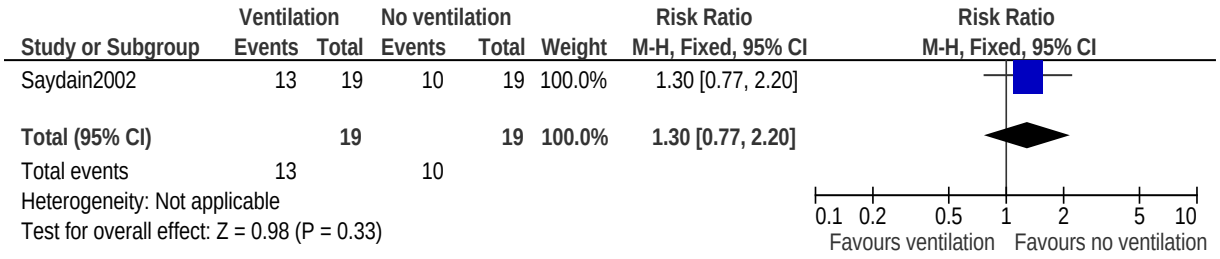
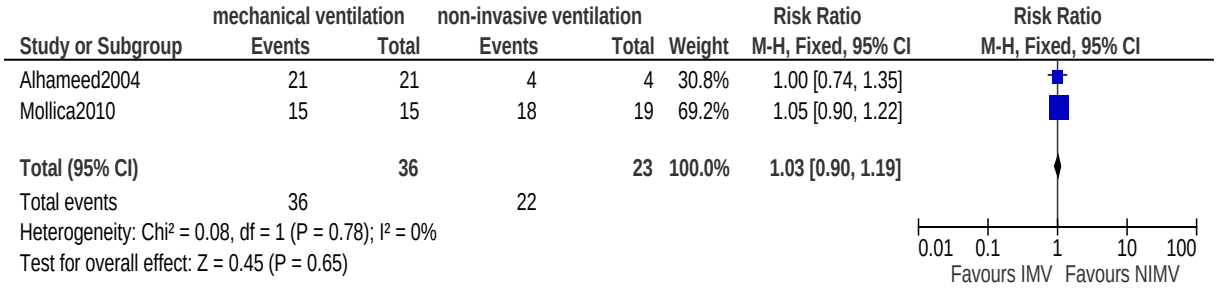


Figure 112: Mortality at 6 months in IPF patients on invasive mechanical ventilation vs. non-invasive mechanical ventilation



E.8 Patient review and follow-up

No relevant clinical studies comparing different timings and delivery of review appointments were identified

Appendix F: Clinical evidence tables

F.1 Diagnosis

F.1.1 Bronchoalveolar lavage

Table 17: Ohshimo 2009 [365]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Ohshimo 2009 [365] Country of study: Germany Study design: retrospective Setting: Ruhrlandklinik, Essen, Germany Duration of follow-up: NR	Patient group: suspected IPF on HRCT Patient characteristics: mean (SD) N: 101 (suspicious IPF based on HRCT findings) Excluded: 17- no evidence of restriction 3- no impairment of gas exchange 5- evidence of collagen vascular disease- associated interstitial pneumonia or drug-induced pneumonia 2- lacked clinical history for IPF N after exclusions: 74 (all had a clinical diagnosis of IPF according to ATS/ERS criteria) M:F: 60:14	All patients HRCT findings were evaluated by observers blinded to BAL results and other clinical data. Intervention: BAL	Final diagnosis Change in diagnosis after BAL	IPF 68 NSIP 3 EAA 3 6/74	Funding: Arbeitsgemeinscaft zur Foderung der Pneumologie an der Ruhrlandklinik (AFPR) Limitations: Concurrent medication use Additional outcomes: BAL findings Notes: Year: 2003-2007

Study details	Population	Methods	Outcome measures	Effect size	Comments
	Age: 69 (8) Smoking status, current/ex/ non: 4/40/29 Duration of symptoms before diagnosis, years: 3.2 (4.5) Relevant concomitant medications, n (%): Corticosteroids and/ or immunosuppressants: 17 (23) Oxygen use: 7 (9) Inclusion criteria: criteria recommended in 2002 ATS/ERS consensus statement				

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

F.1.2 Transbronchial biopsy/ surgical lung biopsy

Table 18: Aalokken 2012[6]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Aalokken 2012[6] Setting: regional and	Patient group: clinical suspicion of ILD who had undergone both HRCT and SLB Inclusion criteria:	All patients underwent SLB (open thoracotomy or thoracoscopy) and thin-section CT.	Histological diagnosis		Funding: NR Limitations: details of clinical information known to
			Sensitivity	73%	
			Specificity	74%	
			PPV	83%	
			NPV	61%	

Study details	Population	Methods	Outcome measures	Effect size	Comments
national centre for chronic lung diseases, Norway 1992-2007 Duration of follow-up: 3-17 years (range), 7.2 (median) Design: retrospective cohort	CT examinations were judged to be consistent The lung disease was not associated with connective tissue disease, environmental exposure and/ or drug toxicity Exclusion criteria: Histopathologic specimens not available or of suboptimal quality All patients n=91 initially, n=64 had a composite reference diagnosis established and were included in the analysis. M/F: 49/42 Mean age: 53.2 years, range 23-79 Follow up: 3-17 years (range), 7.2 (median)	Criteria for CT Images were reviewed separately and in random order by two chest radiologists. Observers were blinded to clinical information and histological diagnosis. CT features were classified according to the Nomenclature Committee of the Fleischner Society. Criteria for histopathology Specimens were retrospectively studied by light microscopy in consensus by two experienced lung pathologists who were blinded to clinical and radiological features. Classification was according to ATS criteria. A composite reference standard was used to			reviewers unclear Additional outcomes: Inter-observer variation for the evaluation of first choice HRCT diagnosis Inter-observer variation for the extent of HRCT abnormalities Thin section CT readings, comparison between UIP and non-UIP patients Sensitivity, specificity, PPV and NPV of CT diagnosis Notes: During the follow-up period 45 patients died and 5 patients underwent lung transplantation due to respiratory failure MDT consisted of a pulmonologist and a radiologist.
			Consensus CT reading		
			Overall correct diagnosis	37/64 (58%), including 26 (63%) in people with UIP	
			Histological consensus (correct diagnosis)	34/64 (53%), including 30 (73%) cases of UIP	
			Diagnostic yield (histology)	64 people with IIP	
			TP	30/64 (73%)	
			TN	4/64	
			FP	6/64	
			FN	unclear	

Study details	Population	Methods	Outcome measures	Effect size	Comments
		provide an overall clinical diagnosis at the end of the study. A multidisciplinary team (pulmonologist and a radiologist). The team was blinded to the results of the retrospective review of the initial thin-section CT scans and retrospective histological evaluation made for the purpose of this study.			

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 19: Coutinho 2008 [89]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Coutinho 2008 [89] Country of study: Portugal	Patient group: diffuse parenchymal lung disease (DPLD) Exclusion criteria: NR Patient characteristics: mean (SD) N: 120	All patients Previous investigations included: Clinical assessment CXR/ CT/ HRCT Bronchoscopic exam and	Mortality Diagnosis	0 IIP 42 Hypersensitivity pneumonitis 21 Pneumoconiosis 18 Sarcoidosis 16 Organizing pneumonia 5	Funding: NR Limitations: Retrospective study- difficult to know the real accuracy of the

Study details	Population	Methods	Outcome measures	Effect size	Comments
Study design: Retrospective review Who was blinded: no-one Setting: Centre of Cardiothoracic Surgery, University Hospital, Coimbra, Portugal Duration of follow-up: NR	Age: 55.8 (14.0) range 17-77 M:F: 50:50 Smoking status (%): 37.5 Immunosuppressed (%): 30.8 Symptomatic (%): 67.5	related procedures (BAL/ TBB) Microbiology culture Intervention: SLB (VATS/ OLB)		Respiratory bronchiolitis 5 Connective tissue associated 4 Amiodarone associated 3 Histiocytosis 2 Eosinophilic pneumonia 1 Others 3	clinical/ imagiological examination due to patients being treated conservatively and others with a correct pathological diagnosis obtained by less invasive procedures not included in the study. Not all patients originated in the same institution, many being referred from other centres, meaning the clinical and imagiological observations were not uniform for all patients, with a probable impact on accuracy.
			Correlation between clinical/ imagiological and histopathological diagnosis	Correct diagnosis 76% (n=80) New diagnosis 21% (n=22) Biopsy inconclusive 3% (n=3)	
			Sensitivity % (95% CI) of clinical diagnosis	67 (57-75)	
			Specificity % (95% CI) of clinical diagnosis	90 (85-93)	
			PPV % (95% CI) of clinical diagnosis	76 (67-84)	
			NPV % (95% CI) of clinical diagnosis	85 (80-89)	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 20: Flaherty 2002 [150]

Study details	Population	Methods	Outcome measures	Effect size	Comments

Study details	Population	Methods	Outcome measures	Effect size	Comments
Flaherty 2002 [150] Country of study: USA Study design: NR Who was blinded: NR Setting: NR Duration of follow-up: NR	Patient group: Inclusion criteria: Not stated Patient characteristics: mean (SD) N: 168 Age: 38.9 (14.8) FEV1 (% predicted): 63.3 (23.4) FEV1/FVC%: 89 (13.9) DLCO (% predicted): 70.5 (23.7)	All patients Underwent surgical lung biopsy	Diagnosis	UIP 106 Fibrotic NSIP 28 Cellular NSIP 5 RBILD/ DIP 22 Hypersensitivity pneumonia 5 Bronchiolitis obliterans with organising pneumonia 1 Unclassified 1	Funding: NHLBI Limitations: includes pre-1995 data Prognostic study Notes: Year 1989-2000

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 21: Ishie 2009 [204]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Ishie 2009 [204] Country of study:	Patient group: patients being monitored in the Department of Thoracic Surgery of the Nereu	The medical charts of patients being monitored in order to diagnose DPLD were evaluated, as were	IPF diagnosed by VAT	14/48 (29.17%)	Funding: NR Limitations: Population -
			intraoperative complications	2 patients (4.17%) required 4-5 cm auxiliary incisions	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Brazil Study design: retrospective Who was blinded: NR Aim: analyze the role of VAT, which is currently widely used, in the diagnosis of DPLD	Ramos Hospital in the city of Florianópolis, located in the state of Santa Catarina, between July of 1999 and July of 2007 Inclusion criteria: being under outpatient follow-up treatment in order to diagnose DPLD; not having received a diagnosis by noninvasive evaluation; not having received a histopathological diagnosis in the transbronchial biopsy, when performed. Exclusion criteria: requiring mechanical ventilation in an intensive care unit being oxygen dependent All patients N: 48 Age range (mean): 20-76 (58.77) Drop outs: 0	the results of the anatomopathological examination of lung biopsy specimens collected through video-assisted thoracoscopy	postoperative complication	1 patient (2.08%) presented with a residual pneumothorax after chest tube removal	hospitalised patients Additional outcomes: gender and age of the patients the distribution of biopsy sites, duration of thoracic drainage in the postoperative period

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 22: Jamaati 2006 [210]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Jamaati 2006 [210] Country of study: Iran Study design: retrospective Who was blinded: no-one Setting: Masih Daneshvari Hospital	Patient group: IPF Inclusion criteria: Not stated Patient characteristics: mean (SD) N: 50 (27M, 23 F) Age: 56.25 (15.86) Clinical features: frequency, % Dyspnoea: 50 (100%) Cough: 45 (90%) Weight loss: 28 (56%) Orthopnoea, PND: 22 (44%) Chest pain: 16 (32%) Oedema: 10 (20%) Haemoptysis: 2 (8%) Clinical signs: frequency, % Crackles: 45 (90%) Tachpnoea: 29 (58%) Cyanosis: 16 (32%) Clubbing : 15 (30%) HRCT pattern Reticular pattern: 21 (42%) Honeycomb: 15 (30%) Ground glass: 3 (6%) Reticulo-nodular: 8 (16%) Increased pleural thickening: 8	All patients Transbronchial biopsy (70%) OLB (26%) Video assisted thoracoscopic lung biopsy (4%)	Diagnosis	All patients showed UIP on microscopy	Funding: NR Limitations: Pathological findings not well described. Additional outcomes: HRCT pattern Notes: Occupational/ environmental exposure described in patient characteristics- some cases may not be IPF.

Study details	Population	Methods	Outcome measures	Effect size	Comments
	(16%) Lymphadenopathy: 7 (14%) Normal: 0 Occupational/ environmental exposure Farming: 9 (18%) Cigarette smoking: 9 (18%) History of baking: 7 (14%) Contact with metal dust: 4 (8%) Contact with chemicals: 1 (2%) Contact with dust: 3 (6%) Contact with asbestos: 1 (2%) Indefinite contact: 16 (32%)				

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 23: Lettieri 2005A [279]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Lettieri 2005A [279] Country of study: USA Study design: retrospective	Patient group: suspected ILD Exclusion criteria: <18 years of age History of biopsy proven ILD	All patients Data were abstracted regarding demographics, factors known to increase perioperative mortality, pulmonary function, spirometry.	Mortality- all patients	4/83 (4.8%) at 30 days 5/83 (6.0%) at 90 days	Funding: NR Limitations: Retrospective study- likely to be confounded by recall and coding bias
			Mortality- IPF patients	3/42 (7.1%) at 30 days 4/42 (9.5%) at 90 days (of these, only one was suspected to have IPF based on clinical and radiographic findings)	
			Mortality- non-IPF	1/41 (2.4%) at 30 days	

Study details	Population	Methods	Outcome measures	Effect size	Comments
cohort Who was blinded: no-one Setting: tertiary care university affiliated medical centre Duration of follow-up: 90 days	Patient characteristics: mean (SD) N: 88 underwent SLB; 5 patients excluded due to incomplete data. Final number: 83 Age: 57.3 (14.2) FVC (% predicted): 69.8 (15.1) FEV1 (% predicted): 67.9 (15.9) DLCO (% predicted): 42.7 (14.8) Male (%): 57.8 Tobacco use(%): 53.0 Supplemental oxygen: 45.8 % Immunosuppressed: 16.9% Mechanically ventilated: 9.6%	It was noted whether the patient required supplemental oxygen at the time of SLB, and whether they were in ICU receiving mechanical ventilation. SLB (OLB 27.7%)	patients	1/41 (2.4%) at 90 days	Small sample size Institution in study not an IPF referral centre Referral for SLB was not protocolled Selection bias may mean that some very ill patients were never considered to be candidates for SLB- may have led to an overestimate of SLB safety
			Diagnosis	IPF: 42/83 Non-IPF: 41/83 40% of subjects in whom IPF was eventually diagnosed per ATS guidelines were thought to have had other conditions pre-operatively.	
			Adverse events	7/83 (8.4%), of which 2 were in IPF patients Acute MI 2 Nosocomial pneumonia 2 Stroke 1 Pancreatitis 1 Prolonged mechanical ventilation 1	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 24: Lettieri 2005 [280]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Lettieri 2005 [280] Country of study: USA Study design: retrospective	Patient group: subjects presenting to the pulmonary clinic with both clinical and radiographic evidence of ILD Inclusion criteria: Not stated Patient characteristics: mean (SD)	All patients Underwent SLB. A general pathologist initially reviewed all SLB specimens. In some instances, specimens were further reviewed by pathologists with expertise	Diagnosis	Achieved in 93.2% of pts by the general pathologist, and in all cases by the specialist UIP 17 (specialists), 22 (general pathologists) NSIP 10 (specialists), 7 (general pathologists) Sarcoidosis 4 (specialists), 0 (general	Funding: NR Limitations: None reported Notes: Gold standard was the findings of the

Study details	Population	Methods	Outcome measures	Effect size	Comments
Setting: Walter Reed Army Medical Centre, Washington DC (large, multidisciplinary, tertiary care referral centre) Duration of follow-up:	N: 83 underwent SLB. Of these, samples from 44 patients were further reviewed by pathologists specialising in pulmonary diseases. N=44 Age: 58.5 (14.2) % male: 47.7% FVC, % predicted: 70.2 (14.3) FEV1, % predicted: 68.6 (15.4) DLCO: 43.7 (13.5) % requiring supplemental O2 at time of biopsy: 54.5%	in ILD. Only those patients whose samples were examined by a pathologist specialising in pulmonary diseases were included in the final cohort. Each patient had multiple sites sampled by either OLB or VATS. The final diagnosis represented the consensus of several pulmonary pathologists.		pathologists) Cryptogenic organising pneumonia 3 (specialists), 3 (general pathologists) Diffuse alveolar damage 2 (specialists), 1 (general pathologists) Infection 2 (specialists), 1 (general pathologists) Malignancy 2 (specialists), 0 (general pathologists) Other 5(specialists) 10 (general pathologists)	specialist pathologist
			Difference in histopathological interpretation between general and specialist pathologists	Occurred in 52.3% of cases (kappa 0.21), leading to a change in clinical management in 60% of cases.	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 25: Oliveira 2011 [366]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Oliveira 2011 [366] Country of study: Brazil Study design:	Patient group: suspected ILD Inclusion criteria: Not stated Exclusion criteria: Incomplete clinical history/ examination	All patients Clinical suspicion of ILD was defined as the presence of dyspnoea or dry cough accompanied by radiological findings of nodules or reticular	Diagnosis	11/56 (19.6%) had a definitive diagnosis of IPF 45/56 non-IPF diagnosis	Funding: None Limitations: Additional outcomes: Sensitivity, specificity, PPV, NPV, likelihood

Study details	Population	Methods	Outcome measures	Effect size	Comments
retrospective Who was blinded: Setting: hospital das Clinicas de Botucatu, Brazil (a tertiary care university hospital) Duration of follow-up: NR	No CT scan Patient characteristics: mean (SD) N: 56 (25F, 31 M) Age: 56 (median), 15-80 (range) Symptoms: dyspnoea (70%), dry cough 59%, weight loss 36%. Smokers: 26/56 (46%) 8/56 (14.3%) had previously undergone SLB for diagnosis- 4 of these had a final diagnosis of IPF	pattern for at least 3 months. Intervention: TBB			ratio and accuracy of radiological changes from 1-6 Notes: Year 1999-2006 Final diagnosis obtained using ATS/ERS criteria 2002 Age range 15-80

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 26: Ooi 2005 [368]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Ooi 2005 [368] Country of study: UK	Patient group: suspected diagnosis of ILD Inclusion criteria: Diffuse ILD Patient characteristics: mean (SD)	All patients Preoperative investigations included: extensive clinical evaluation and HRCT	Diagnosis	(Histological diagnosis not consistent with ILD: 8) ILD: 70 26/70 (37.1%) UIP 13/70 (18.6%) non-specific pulmonary fibrosis	Funding: NR Limitations: None reported

Study details	Population	Methods	Outcome measures	Effect size	Comments
Study design: retrospective Who was blinded: no-one Setting: Papworth Hospital, Cambridge Duration of follow-up:	N: 70 (57 M, 13 F) Age: 56 (mean), range 20-89	Open lung (15/70) or VATS biopsy(55/70). there were no conversions from VATs to OLB.		31/70 (44.3%) other diagnosis	
			Difference between pre-operative clinico-radiological and final histological diagnosis sufficient to change prognosis and definitive management	19 patients (27.1%) Malignancy was ruled out in 6 patients (8.6%) Infection was ruled out in 7 patients (10%)	
			Mortality	1 patient (1.5%) due to adult respiratory distress syndrome	
			Adverse events	OLB: 0 VATS: 1 death, 1 pneumothorax, 1 haemothorax, 2 urinary retention	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 27: Peckham 2004 [379]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Peckham 2004 [379] Country of study: USA Study design: Retrospectiv	Patient group: patients undergoing lung biopsy for the diagnosis of ILD Exclusion criteria: Patient characteristics: mean (SD) N: 26 (18M, 8 F) 88% were current or former	All patients SLB	Diagnosis	14/26 (53.8%) UIP 5/26 NSIP 2/26 sarcoidosis 2/26 neoplastic disease 1/26 end stage fibrosis 1/26 cryptogenic organising pneumonia	Funding: NR Limitations: Small sample size Study design-retrospective more prone to bias

Study details	Population	Methods	Outcome measures	Effect size	Comments
e Who was blinded: no-one Setting: United States army tertiary care medical centre, USA Duration of follow-up: 60 days	smokers		Sensitivity	HRCT 71% (51-92%) ATS clinical criteria 71% (51-92%)	Study performed in tertiary care therefore not applicable to community settings Notes: Gold standard was histological diagnosis in the absence of known aetiologies
			Specificity	HRCT 67% (39-86%) ATS clinical criteria 75% (47-92%)	
			PPV	HRCT 71% (51-92%) ATS clinical criteria 77% (50-92%)	
			NPV	HRCT 67% (39-86%) ATS clinical criteria 73% (54-86%)	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 28: Rena 1999 [408]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Rena 1999 [408] Country of study: Italy	Patient group: ILD of unknown aetiology Inclusion criteria: Not stated Patient characteristics: mean (SD) N: 58 (33M, 25F)	All patients Preoperative investigations included: PFTs, HRCT, serological evaluation of Rh factor, ANA, anti-nuclear cytoplasmic antibodies,	Diagnosis	IPF: 14 Other diagnosis: 44	Funding: NR Limitations: Biopsy not compared to a reference standard
			Mortality	0	
			Adverse events	2 (prolonged air leak > 5 days)	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Study design: prospective cohort Who was blinded: no-one Setting: Duration of follow-up: NR	Age: 49.6 (12.0)	angiotensin converting enzyme. Bronchoscopy and BAL were carried out and specimens sent for cell count, cytological examination, lymphocyte subtyping and microbiological studies. Video-assisted thoracoscopic lung biopsy			Study is pre-2002 therefore ATS/ERS criteria not used

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 29: Sigurdsson 2009 [442]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Sigurdsson 2009 [442] Country of study: Iceland Study design: retrospective	Patient group: suspected ILD Exclusion criteria: people with a solitary pulmonary nodule or patients in whom the surgery was used to remove foreign bodies or for treatment of recurrent pulmonary infections.	All patients Information collected: Clinical symptoms, smoking history, clinical examination, spiromentry, DLCO, lab results, chest radiographs CT results,	Mortality	2/73 (3%) at 30 days 3/73 (4%) at 90 days	Funding: NR Limitations: not all patients had a CT scan (81%) prior to biopsy Additional outcomes: Notes:
			Diagnosis	UIP23/72 (32%), of which 12 were nonspecific fibrosis (16% of total) Noninterstitial diagnosis: 8/73 (11%)	
			Adverse events	Total 12/73 (16%) Prolonged air leakage 9/73 (12%)	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Setting: Landspitali University Hospital Duration of follow-up: NR	Patient characteristics: mean (SD) N: 73 Age: 57.3 years (mean), 20-88 (range) M 58%, F 42% History of smoking 75% Heavy smoker (>20 pack years) 53% Previous Ix: CXR: all patients CT scan 59/73 (81%) TBB 51/73 (70%)	bronchoscopy results, indication and relative contraindications for the surgical biopsy, clinical diagnosis before and after the biopsy. Biopsy from VATS or OLB. OLB: 45 (62%), VATS that were converted to thoracotomy: 3, VATS (85% of operations after 2005). (VATS increasingly used after 1991). All lung specimens were read by one of the attending pathologists and frequently reviewed by one or more additional pathologists before codes were assigned.		Need for mechanical ventilation 3/73 (4%) Pneumonia 3/73 (4%) Acute exacerbation of respiratory failure 2/73 (3%) Other 1/73 (1%)	SNOMED coding used for pathology specimens

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 30: Slodkowska 2000 [444]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Slodkowska 2000 [444] Country of	Patient group: 6 people with clinical diagnosis of IPF and 8 people with UIP	All patients Clinical diagnosis of IPF/UIP was based on	Diagnostic yield	Histopathologic results - UIP in 7/14 patients Clinical re-assessment (based on HRCT	Funding: NR

Study details	Population	Methods	Outcome measures	Effect size	Comments
study: Poland Study design: Retrospective Who was blinded: not reported Setting: analysis of patient records from Chinese literature and data from Drum Tower Hospital, Nanjing, China Duration of follow-up: Follow-up ranged from 1-4 years.	Exclusion criteria: people without any underlying medical conditions or potential causes of pulmonary abnormalities e.g. connective tissue disease, exposure to organic or inorganic dust, toxic fumes and history of specific drug intake (no further details reported) Patient characteristics: mean (SD) N: 14 (6F and 8M) Age range: 28-73yrs	clinical symptoms, chest radiographs, HRCT and lung function tests. Histologic re-examination of open lung biopsy specimens performed for all patients Separate analysis of HRCT findings. No further details.		and pathology reports - UIP 12/14 patients Histopathology and HRCT analysis - UIP 7/14 patients	Limitations: Specific time period between clinical diagnosis, histologic and HRCT analysis not reported. Small sample size Study is pre-2002 therefore ATS/ERS criteria not used Notes: Authors note that discrepancy between histology and HRCT was due to a sampling problem observed in 2/12 (14%) patients. Authors conclude this is due to disease progression.

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 31: Trahan 2008A [477]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Trahan 2008A [477] Country of study: USA Study design: retrospective Setting: data used from Mayo clinic database as well as 5 patients from Mayo Clinic Duration of follow-up: NR	Patient group: people with a clinical diagnosis of chronic hypersensitivity pneumonia (HP) Exclusion criteria: NR Patient characteristics: mean (SD) N: 15	All patients SLBs were reviewed retrospectively without knowledge of the clinical diagnosis	Diagnosis from 31 biopsy specimens	HP 24 UIP 5 NSIP 1 (cellular) Other 1 (emphysema)	Funding: NR Limitations: small sample size Specific antigenic exposures / precipitating antibodies were identified in some pts Notes: year 1997-2005

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 32: Vansteenkiste 1999 [486]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Vansteenkist	Patient group: ILD, not specified	All patients	Adverse events	Air leak: 7	Funding: NR

Study details	Population	Methods	Outcome measures	Effect size	Comments
e 1999 [486] Country of study: Belgium Study design: NR Who was blinded: no-one Setting: NR Duration of follow-up: NR	after clinical assessment Inclusion criteria: Not stated Patient characteristics: mean (SD), range N: 24 (11M, 13F) Age: 52.3 (16.7) FVC: 88 (18%)56-132 FEV1: 81 (14%) 54-109 TLC: 85 (16%) 64-129 DLCO: 53 (21%) 28-94 A previous BAL yielded nonspecific results in 17 patients and TBB in 11. 5 patients had been previously treated with corticosteroids	8 patients had a thoracotomy with OLB and 5 had a VATS with a wedge biopsy by stapler All biopsy samples were examined prospectively and blinded to the clinical data by one lung pathologist.	 Mortality	Bleeding: 1 Fever: 3 3 (at follow-up)	Limitations: Biopsy not compared to a reference standard Study is pre-2002 therefore ATS/ERS criteria not used Additional outcomes: Histopathological diagnosis by biopsy location

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 33: Yamagutchi 2004 [501]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Yamagutchi 2004 [501] Country of	Patient group: ILD diagnosed by chest radiography and computed tomography	All patients	Diagnosis (diagnostic yield 100%)	Idiopathic interstitial pneumonia (IIP)20 IPF 12	Funding: NR

Study details	Population	Methods	Outcome measures	Effect size	Comments
study: Japan Study design: retrospective Setting: not stated Duration of follow-up:	Exclusion criteria: Patient characteristics: mean (SD) N: 30 (18M, 12 F) Age:56.7 Preoperative vital capacity 80% Preoperative FEV1 83.6%	Elective VATLB		Non-specific interstitial pneumonia (NSIP) 7 Acute interstitial pneumonia 1 Other diagnosis 10	Limitations: retrospective study, small sample size Notes: Year 1994-2002
			Change in treatment following histological diagnosis?	Total: yes 17 (57%), no 13 (43%) IIP: yes 11 (55%), no 9 (45%) IPF: yes 5 (42%), no 2 (29%) NSIP: yes 5 (71%), no 2 (29%) Acute interstitial pneumonia: yes 1 (100%), no 0 (0%)	
			Adverse events	3/30 (10%) 2 acute respiratory failure 1 prolonged air leak	
			Mortality	0	
			5 year survival rate (%)	Total: 78.8 Those who had treatment change: 69.8 Those who did not have treatment change 88.9	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

F.1.3 Multi-disciplinary team

Table 34: Flaherty 2003A [149]

Study details	Patients	Methods	Outcome measures	Effect size	Comments

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Flaherty 2003A [149] Country of study: USA Study design: Retrospective Who was blinded: Setting: Aim: examines whether HRCT features add prognostic information to the histological classification in the differential diagnosis of UIP and	Patient group: consecutively referred Patients from the University of Michigan Specialized Center of Research in the Pathobiology of Fibrotic Lung Disease database. Who underwent surgical lung biopsy between October 1989 and February 2000. Inclusion criteria: people with a histological diagnosis of UIP or NSIP (by surgical lung biopsy) HRCT scan within 6 months of the biopsy Exclusion criteria: Associated collagen vascular illness All patients N: 73 (histological UIP) 23 (histological NSIP) Age (mean±SD): NR Drop outs: 0	Radiological classification Two thoracic radiologists independently reviewed each HRCT scan and recorded each case as either definite UIP, probable UIP, indeterminate (equal probability of UIP or NSIP), probable NSIP, definite NSIP. The finding felt by the radiologists to indicate probable or definite UIP was honeycombing, as this finding correlates strongly with pathological fibrosis and impaired survival. The absence of honeycombing, the presence of ground glass opacity, and an apical or non-subpleural distribution favoured NSIP Pathological classification Three pathologists blinded to the clinical and radiological features reviewed the biopsy	Differential HRCT consensus diagnosis of people with a histological diagnosis of UIP	Definite UIP : 16/73 Probable UIP : 11/73 Indeterminate: 20/73 Probable NSIP : 17/73 Definite NSIP : 9/73	Funding: NR Limitations: Study design-retrospective more prone to bias Notes: Interobserver agreement of the radiological diagnoses was described using kappa and weighted kappa statistics, where weighted kappa statistics confer partial agreement for assignment of adjacent diagnoses—for example, definite and probable UIP, or probable UIP and indeterminate assignments.23 Interobserver agreement between radiologists was first evaluated across all five diagnostic categories (definite UIP, probable UIP,
			Radiologist complete agreement	35/96 (36%) Kappa = 0.20 p<0.0001 Weighted kappa = 0.43 p<0.0001	
			Radiological diagnosis of definite /probable UIP	27/73 total cases of histologically diagnosed UIP	
			Radiologists specificity	100%	
			Radiologists sensitivity	37% (SD 6)	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
NSIP, and determines whether the current radiological criteria for NSIP are useful in histologically proven cases of NSIP		specimens. Each specimen was assigned a histological diagnosis of UIP or NSIP using defined criteria. A patient received a diagnosis of UIP when one or more biopsy specimens showed UIP. Cases of cellular NSIP (n=3) and fibrotic NSIP (n=20) were collectively classified as NSIP			indeterminate, probable NSIP, and definite NSIP).

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 35: Flaherty 2007[152]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Flaherty 2007 [152] Country of study: USA Study design:	Patient group: Data from patients referred to the University of Michigan Specialized Centre of Research in the Pathobiology of Fibrotic Lung Disease between August 2002 and December 2003. People with suspected IIP were referred to the study centre by participants in the University of Michigan Fibrotic	Patients underwent a history, physical examination, complete pulmonary function testing, HRCT, and SLB. Case information was provided to three groups (community 1, community 2, and the University of Michigan) on separate	Inter observer Agreement κ Score Step 5: Consensus diagnosis Academic centre	Clinical: 0.71 (± 0.03 SE) Radiological: 0.55 (± 0.08 SE) Pathology: 0.57 (± 0.05 SE)	Funding: National institute of health, National Heart, Lung and Blood Institute grants Limitations: Study design- retrospective more prone to bias
			Inter observer Agreement κ Score Step 5: Consensus diagnosis Community centre	Clinical: 0.44 (±0.07 SE) Radiological: 0.32 (±0.11 SE) Pathology: 0.41 (±0.13 SE)	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Retrospective review Who was blinded: NR Setting: 2 community locations and 1 academic location Aim: Evaluated the agreement in classification of people with suspected IIP in community and academic settings. And examined the influence	Lung Disease Network Inclusion criteria: NR Exclusion criteria: People without an HRCT scan or an SLB were excluded All patients N: 39 Age (mean±SD): NR Drop outs: 0	days. Participants at the University of Michigan were expert clinicians, radiologists, and pathologists from five centres (within and outside the United States). On average, participants at the University of Michigan had been in practice longer and spend a greater amount of time in the evaluation and treatment of people with interstitial lung disease The cases were presented with the same information and in the same order at each institution. Provided participants incremental information through five stages clinicians and radiologists independently reviewed HRCT, clinicians and radiologists independently reviewed clinical information & HRCT clinicians and radiologists	Clinicians: Sensitivity without MDT#	Community : 65%-74% Academic: 50%-55% Overall:55%- 62%	Notes: McNemar tests were used to test whether two probabilities of agreement conducted during different steps or by different raters were equal. A κ statistic allowing for multiple raters was used to assess agreement in diagnosis. κ Scores are rated as almost perfect agreement (above 0.8), substantial agreement (scores between 0.6 and 0.8), moderate agreement (scores between 0.4 and 0.6), fair agreement (scores between 0.2 and 0.4), slight agreement (scores between 0.0 and 0.2), and poor agreement (scores below 0.0)
			Radiologists: Sensitivity without MDT#	Community : 80%- 85% Academic: 48%-73% Overall: 64%-79%	
			Pathologists: Sensitivity without MDT#	Community : 90%- 92% Academic: 86%-98% Overall: 96%-88%	
			Clinicans and radiologists Sensitivity without MDT#	Community : 71%- 78% Academic: 49%-60% Overall: 58%-67%	
			Clinicans, radiologists and pathologist: Sensitivity without MDT#	Community : 82%- 87% Academic: 72%-78% Overall: 76%-81%	
			Clinicians: Specificity without MDT#	Community : 72%- 81% Academic: 88%-94% Overall: 83%-90%	
			Radiologists: Specificity without MDT#	Community : 65%- 78% Academic: 97%-98% Overall: 82%-88%	
			Pathologists: Specificity without MDT#	Community :43%- 53% Academic: 67%-81% Overall: 59%-72%	
			Clinicans and	Community :70%- 80%	

Study details	Population	Methods	Outcome measures	Effect size	Comments
of an iterative diagnostic approach on diagnostic agreement in a community compared with an academic setting, and addressed features that influenced diagnostic approaches		discussed, as a group, the clinical and HRCT features As this was occurring, the pathologists were independently reviewing SLB specimens and assigning an independent histopathologic diagnosis. Clinicians, radiologists, and pathologists discussion of the findings of HRCT, clinical data and SLB. an attempt was made to reach a consensus diagnosis.	radiologists Specificity without MDT#	Academic: 90%-95% Overall: 82%-89%	An estimating equation approach to the analysis of correlated κ statistics was used in comparisons of κ statistics estimated throughout the study and in producing confidence intervals for the κ statistics # NCGC calculated using data reported in paper
			Clinicans, radiologists and pathologist: Specificity without MDT#	Community :64%- 72% Academic: 83%-90% Overall: 78%-84%	
			Clinicians: Sensitivity with MDT#	Community :85%- 87% Academic: 74%-100% Overall: 78%-96%	
			Radiologists: Sensitivity with MDT#	Community :90%- 92% Academic: 53%-77% Overall: 71%-85%	
			Pathologists: Sensitivity with MDT#	Community :95%- 100% Academic: 80%-98% Overall: 85%-99%	
			Clinicians and radiologists Sensitivity with MDT#	Community :87%- 89% Academic: 69%-94% Overall: 76%-92%	
			Clinicians, radiologists and pathologist: Sensitivity with MDT#	Community :89%- 92% Academic: 73%-96% Overall: 79%-94%	
			Clinicians: Specificity with MDT#	Community :67%- 81% Academic: 91%-97% Overall: 83%-92%	

Study details	Population	Methods	Outcome measures	Effect size	Comments
			Radiologists: Specificity with MDT#	Community :65%- 84% Academic: 93%-94% Overall: 79%-89%	
			Pathologists: Specificity with MDT#	Community :59%- 78% Academic: 77%-94% Overall: 71%-89%	
			Clinicians and radiologists Specificity with MDT#	Community :66%- 83% Academic: 91%-96% Overall:67%-94%	
			Clinicians, radiologists and pathologist: Specificity with MDT#	Community :64%- 81% Academic: 87%-95% Overall:78%-90%	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 36: Hunninghake 2001[198]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Hunninghake 2001 [198] Country of study: USA	Patient group: All new patients suspected of having IPF were entered into the study if their medical condition did not preclude performing the biopsy	Patients had a HRCT scan and a bronchoscopy with a transbronchial lung biopsy. The transbronchial biopsy was performed to detect lung diseases other than	Overall IPF Diagnosis Clinical core	Sensitivity: 39/54 (72%) Specificity: 31/37 (84%) Accuracy: 70/91 (77%) Positive Predictive Value: 39/45 (87%)	Funding: NHLBI SCOR program on interstitial lung disease Limitations: none
			Overall IPF Diagnosis Radiology core*	Sensitivity: 41/53 (77%) Specificity: 26/36 (72%) Accuracy: 67/89 (75%) Positive	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Study design: prospective, blinded study Who was blinded: NR Setting: eight referring centres Aim: determined the value of clinical and radiologic findings for the diagnosis of IPF.	Inclusion criteria: Patients able to undergo biopsy Exclusion criteria: People with an underlying connective tissue disorder Exposure to environmental agents or drugs known to cause pulmonary fibrosis Other underlying disorders known to cause pulmonary fibrosis All patients N: 91 patients Age (mean±SD): NR Drop outs: 0	IPF. If the transbronchial biopsy did not provide a specific diagnosis, patients underwent a surgical (open or thoracoscopic) lung biopsy. The lung HRCT scan was not used to determine if a patient should undergo a surgical biopsy. Before the surgical biopsy but after the results of the lung HRCT scan and transbronchial biopsy, one pulmonologist at each of the referring centres rated the certainty of the diagnosis of IPF (as certain, uncertain, or unlikely) and provided an overall clinical diagnosis, even if the diagnosis was uncertain. The centre investigators could use any clinical information that was available for the patient to provide this assessment. No predetermined clinical or radiologic criteria were used to make a clinical		Predictive Value: 41/48 (85%)	Additional outcomes: Sensitivity, specificity, accuracy and positive predictive value of a confident diagnosis of IPF (excluding cases where the investigator was uncertain of the diagnosis of IPF) Bayesian posterior conditional predicative probability of IPF (A prior probability of 0.60 of having IPF among new suspected patients that presented for diagnosis was used in the calculation of the posterior probability.) Notes: * Excludes two patients for whom the radiology core provided no diagnosis The kappa coefficient used to measure agreement within the cores was based on
			Overall IPF Diagnosis Referring centre	Sensitivity: 46/54 (85%) Specificity: 16/37 (43%) Accuracy: 62/91 (68%) Positive Predictive Value: 46/67 (69%)	
			Probability Of Agreement Within The Cores IPF versus Non-IPF Agreement	Clinical: 0.79 Radiological: 0.77 Pathology: 0.85	
			Probability Of Agreement Within The Cores IPF versus Non-IPF Kappa score	Clinical: 0.59 (±0.06 SE) Radiological: 0.54 (±0.06 SE) Pathology: 0.68 (±0.06 SE)	
			Probability Of Agreement Within The Cores Specific Diagnosis of ILD Agreement	Clinical: 0.49 Radiological: 0.54 Pathology: 0.72	
			Probability Of Agreement Within The Cores Specific Diagnosis of ILD Kappa score	Clinical: 0.32 (±0.05 SE) Radiological: 0.31 (±0.05 SE) Pathology: 0.55 (±0.05 SE)	

Study details	Population	Methods	Outcome measures	Effect size	Comments
		diagnosis or to determine the level of certainty of the diagnosis of IPF. The following information was provided by the referring centres for review by a clinical core of three pulmonologists: presence and duration of cough; presence and duration of dyspnea; history of smoking; history of fever, weight loss, myalgias, arthralgias, rash, and arthritis; presence of finger clubbing; and pulmonary function tests. The clinical core directly evaluated chest radiographs and HRCT scans. Each independently rated their certainty of the diagnosis of IPF (as certain, uncertain, or unlikely) and provided an overall clinical diagnosis, even if the diagnosis was uncertain. A core of four chest radiologists independently evaluated the HRCT scans.			the form proposed by Kraemer which allowed for unequal numbers of observations per subject. The probability of agreement between any two members of a core, estimated as the average proportion of concordant pairs for all possible pairings of raters per subject, was also estimated. Using the pathology diagnosis of IPF as the gold standard, sensitivity, specificity, accuracy, and positive predictive value of the diagnosis of IPF of the cores and centres were calculated.

Study details	Population	Methods	Outcome measures	Effect size	Comments
		No clinical information was provided. Each rated their certainty of the diagnosis of IPF (as certain, uncertain, or unlikely), and provided an overall clinical diagnosis, even if the diagnosis was uncertain. A core of three lung pathologists independently evaluated the same sets of pathology slides. No clinical information was provided. They provided an overall pathologic diagnosis, and if they were unsure of the diagnosis, they provided a secondary diagnosis.			

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 37: Lynch 2005 [292]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Lynch 2005 [292]	Patient group: Patients diagnosed with IPF, enrolled into a phase 3 RCT for IFN-	Assessment by Study-Site Radiologists Using defined criteria,	Diagnosis of the first two readers Study site vs Core	Consistent with IPF: 256 (81.3%) Inconsistent with IPF: 15 (4.8%) Lack of agreement: 44 (14.0%)	Funding: NR Limitations:

Study details	Population	Methods	Outcome measures	Effect size	Comments
Country of study: USA, Europe, Canada, and South Africa (RCT) Study design: Retrospective review of RCT data Who was blinded: Core radiologists Setting: Aim: To describe HRCT features in patients with mild to moderate IPF, compare diagnostic evaluations	y1b, who had a baseline HRCT scan available for evaluation Inclusion criteria: Baseline HRCT was performed within 60 days before the first dose of study drug in the phase 3 trial. Exclusion criteria: NR All patients N: 315 Age (mean±SD): NR Drop outs: 0	radiologists were asked to determine if either "definite" or "probable" IPF was present. A radiographic diagnosis of "definite IPF" required all three of the following criteria: presence of reticular abnormality and/or traction bronchiectasis with basal and peripheral predominance; presence of honeycombing with basal and peripheral predominance; absence of atypical features, such as micronodules, peribronchovascular nodules, consolidation, isolated (nonhoneycomb) cysts, extensive ground glass attenuation, or extensive mediastinal adenopathy. The presence of the first and third criterion only qualified as "probable" IPF (i.e., honeycombing was	radiologists		Clinical information may have been provided and the study-site radiologists knew that IPF was a consideration. The core radiologists were blinded to clinical data and treatment group assignment; however, they knew that the patients had met non-radiologic inclusion criteria for the study, and that a study-site radiologist had interpreted the HRCT scan as at least probable IPF on the basis of predefined criteria. Notes: The simple κ coefficient, ranging from –1 to +1, was used to assess the degree of interrater agreement in specific comparisons. The Wilcoxon rank
			Consensus diagnosis of the three readers Study site vs Core radiologists	Consistent with IPF: 283 (89.8%) Inconsistent with IPF: 30 (9.5%) Lack of agreement: 2 (0.6%)	
			Concordant interpretations by the first two readers	271/315 (86.0%) K = 0.33 (95% CI, 0.18–0.48)	
			Classification of definite IPF cases by core radiologist	Consistent with IPF 245/263 (93.2%) p = 0.001	
			Classification of probable IPF cases by core radiologist	probable IPF: 37/49 (75.5%) p = 0.001	
			Agreement with IPF diagnosis by core radiologists according to study site location (academic/community)	Academic: 206 /228 (90.4%) Community: 76/84 (90.5%) p = 1.0	
			Histologic confirmation of UIP on SLB	205/315 (65%)	
			HRCT classification of IPF diagnosis by core radiologist consensus of cases with histologically confirmed UIP on	Consistent with IPF: 181/205 (88.3%) Inconsistent with IPF: 24/205 (11.7%)	

Study details	Population	Methods	Outcome measures	Effect size	Comments
by a radiology core (three thoracic radiologists) with those by studysite radiologists, correlate baseline clinical and physiologic variables with HRCT findings, and evaluate their association with mortality		not present). Assessment by Core Radiologists After the completion of the trial, a core panel of three thoracic radiologists independently review the baseline HRCT scans. Two core radiologists independently scored the baseline HRCT on a standardized form. The HRCT image was assessed for the presence and extent of ground glass attenuation, reticulation, honeycombing, decreased attenuation, centrilobular nodules, other nodules, consolidation, and emphysema. The extent of these abnormalities and the overall extent of fibrosis were determined for each entire lung using a 4-point scale 0 = no involvement 1 = 1–25% involvement 2 = 26–50% involvement	SLB HRCT classification of IPF diagnosis by core radiologist consensus of cases with no biopsy	 Consistent with IPF: 102/110 (93%) Inconsistent with IPF: 6/110 (5%)	sum, Spearman rank order correlation, and Fisher's exact tests were used for statistical comparisons of selected clinical, histologic, and HRCT characteristics, as appropriate.

Study details	Population	Methods	Outcome measures	Effect size	Comments
		3 = 51–75% involvement 4 = 76–100% involvement The presence or absence of upper or lower lobe volume loss, traction bronchiectasis, crazy paving, tree in bud, bronchiolectasis, and mosaic attenuation was also assessed, and the predominant pattern (i.e., ground glass/ reticulation/honeycombing vs. nodules/mosaic attenuation/ emphysema/ other) was determined. Each HRCT was classified by at least two core radiologists as typical IPF, atypical IPF, or inconsistent with IPF using usual diagnostic evaluation processes without pre-specified criteria for the study. A third core radiologist evaluated the scan if the first two readers did not agree, and the consensus diagnosis was based on agreement of at least two readers.			

Study details	Population	Methods	Outcome measures	Effect size	Comments
		Only two readers were used for pattern extent scores, including honeycombing. Neither discussion nor adjudication was used for any result. In the event of disagreement between the readers, the result was recorded as missing.			

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 38: Raghu 1999 [402]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Raghu 1999 [402] Country of study: USA Study design: Prospective Who was blinded:	Patient group: all symptomatic, adult, untreated people with ILD consecutively referred to a senior ILD specialist for diagnostic evaluation of new-onset ILD without a specific diagnosis at the University of Washington Medical Centre in Seattle Inclusion criteria: Exclusion criteria:	All patients referred during the period from 1992 to 1997 for further diagnostic evaluation of nonspecific ILD were considered potential candidates. Patients meeting the criteria were prospectively evaluated by the senior ILD specialist A detailed and thorough clinical assessment was	Histological diagnosis of IPF	IPF= 29/59	Funding: NR Limitations: Referral of patients from 1992-1997 (pre 1995 outdated?) Notes: The histologic features of SLB were used as the reference standard for an accurate diagnosis to compare
			Clinical diagnosis of ILD other than IPF	Accuracy = 61% of cases Sensitivity = 88.8% Specificity = 40% Positive predictive value = 94% Negative predictive value = 25%	
			Clinical diagnosis of IPF	Accuracy = 62% of cases Sensitivity = 62%% Specificity = 97% Positive predictive value = 95% Negative predictive value = 73%	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Reviewers Aim: tested the hypothesis that a clinical diagnosis based on thorough clinical assessment including HRCT and bronchoscopy findings is both sensitive and specific when compared with the histopathologic diagnosis.	had an established diagnosis based on accepted histologic criteria prior to referral had a diagnostic transbronchial lung biopsy (TBBX) had an established diagnosis of systemic lupus erythematosus, progressive systemic sclerosis, rheumatoid arthritis, dermatopolymyositis (based on accepted diagnostic criteria defined by American Rheumatological Association) had abnormal BUN and creatinine; had a history of having been treated for ILD; had clinical evidence of advanced IPF (clinically advanced IPF was defined as (1) an unexplained insidious onset of breathlessness with exertion with or without a cough of . 3 years' duration; (2) physical findings of late inspiratory crackles at both lung bases with or without clubbing; (3) chest radiographic and/or HRCT evidence of progressive intralobular and interstitial reticular opacities other than ground glass; irregular interlobular septal thickening, and	performed which included examination; and review of laboratory data, pulmonary function tests, bronchoscopy, and chest radiograph and HRCT findings. The histologic features of TBBX in patients who had undergone bronchoscopy were included in the assessment. Immediately following the review of all subjective and objective findings, the specialist documented the most likely specific diagnosis based on his overall clinical assessment. Histopathologic specimens from subjects who had undergone TBBX by referring community pulmonologists were reviewed by our pulmonary pathologist. The cellular analysis of BAL was not included in the assessment. The chest radiographs and HRCT scans were also read	Radiological diagnosis of diagnosis of ILD other than IPF	Accuracy = 58% of cases Sensitivity = 59% Specificity = 40% Positive predictive value = 91% Negative predictive value = 8%	and confirm the clinical and radiologic diagnoses made prior to SLB
			Radiological diagnosis of IPF	Accuracy = 76% of cases Sensitivity = 78.5% Specificity = 90% Positive predictive value = 88% Negative predictive value = 82%	

Study details	Population	Methods	Outcome measures	Effect size	Comments
	diffuse honeycombing in both lungs (not restricted to the subpleural and lower lung zones) associated with traction bronchiectasis on HRCT; had evidence of overt right or left heart failure on physical examination; refused SLB All patients N: 59 Age range (median): 24-78 (53) Drop outs: 0	independently by a senior chest radiologist who made a most likely specific diagnosis based solely on radiographic and HRCT features. The radiologist was only aware that the chest radiographs and HRCT scans were being obtained to rule out ILD. Prior to SLB, neither the radiologist's report nor the clinical diagnosis independently made by the ILD specialist was made available to one another or to the pathologist. All consenting patients in whom a diagnosis was not clearly established by characteristic histologic features on TBBX underwent SLB within 1 month of their initial clinical assessment. The biopsy slides were interpreted by a senior pulmonary pathologist. The pathologist was aware that the SLB was obtained for diagnosis of ILD, but			

Study details	Population	Methods	Outcome measures	Effect size	Comments
		was blinded to all other details of the clinical findings and diagnosis made independently by the clinician and the chest radiologist.			

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 39: Spencer 2011[446]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Spencer 2011[446] Setting: North-West Lung Centre, South Manchester University hospital, UK (a large university teaching hospital with tertiary and quaternary services for respiratory medicine)	Patient group: suspected IPF (referral by chest physician) Inclusion criteria: NR Exclusion criteria: NR All patients N=170 reviewed by the ILD MDT N=161 included in analysis Age: 56 (mean, 15-81 (range) M/F: 92 (57%)/ 69 (43%) Patients were referred from 31 different hospitals, mainly district general, but some teaching hospitals with tertiary care	The clinical history, physiological data, radiology and pathology samples, where available, were reviewed by the MDT (2 specialist ILD physicians, 2 thoracic radiologists, 2 pathologists with an interest in pulmonary disease and an ILD specialist nurse) and a consensus diagnosis was reached in each case. On some occasions a single consensus diagnosis could not be reached, in which case a differential diagnosis was given.	Referral centre: 67 definite IPF, 2 possible IPF	2 possible IPF changed to other diagnoses by MDT 27/67 (40%) of 'definite' IPF were changed to other diagnoses, 10/27 (37%)of which were NSIP	Funding: NR Limitations: a lung biopsy was available in 81/161 (50%) of cases, 6 of which were taken after referral to the MDT and were therefore not reviewed by the referring centre therefore the MDT did not used the same criteria to diagnose each patient Additional outcomes: IPF diagnosis changed/
			Histological diagnosis Available in 38/67 (57%) 21/27 (78%) referred as 'definite' IPF but whose diagnosis had changed, had a lung biopsy to review	Lung biopsy report changed in 14/21 cases (67%)	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Duration of follow-up: Design: retrospective cohort	services Had HRCT of the thorax and their cases had been reviewed by an ILD physician.				unchanged by: patients age Number of months from MDT to follow-up Lung function at time of MDT meeting Change in HRCT report following MDT Change in pathology report following MDT Number of cases agreed/ disagreed between centres Survival benefit from change of diagnosis from IPF to other ILD Notes: some patients were <18 years old The MDT consisted of 2 specialist ILD physicians, 2 thoracic radiologists, 2 pathologists with an interest in pulmonary disease and an ILD specialist nurse, all of

Study details	Population	Methods	Outcome measures	Effect size	Comments
					whom, bar 1 chest physician, had more than 10 years experience in a tertiary referral ILD clinic.

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 40: Sumikawa 2008[454]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Sumikawa 2008 [454] Country of study: Japan Study design: retrospective review Who was blinded: No blinding	Patient group: 154 patients who underwent surgical biopsies at three institutions and who met the clinical and histologic criteria for diagnosis recommended by the ATS/ERS consensus classification of the IIPs were identified. Of which only 112 cases confirmed as confident UIP by a second pathologist where studied Inclusion criteria: NR Exclusion criteria: NR	Patient selection: All 154 cases were originally diagnosed histologically as diagnostic of UIP by a lung pathologist at each of the contributing institutions. All biopsy specimens were also reviewed by a second lung pathologist and classified into the following four categories by the certainty of the diagnosis of UIP: confident UIP, probable UIP, probably not UIP	Classification by second lung pathologist(patient selection)	Confident UIP: 112 cases (73%) Probable UIP: 19 cases (12%) Probably not UIP: 16 cases (10%) Confident not UIP: 7 cases (5%)	Funding: NR Limitations: All radiologists and the pathologist were informed about pathological and clinical UIP diagnosis of the patient Additional outcomes: The relationship between survival duration and the three CT categories as subtypes was
			Radiologists classification of UIP	Definite UIP: 33/112(34%) Consistent with UIP: 36/112 Suggestive of alternative diagnosis: 21/112 (21%) Unclassified findings: 8/112 (8%)	
			The inter-observer agreement of CT diagnosis into consistent with UIP (definite or probable) or suggestive of	moderate (k 5 0.60)	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Aim: to revisit the thin-section CT findings of IPF and to clarify the correlation between CT findings and mortality	All patients N: 154 (pathological review) 112 (radiological review) Age (mean±SD): NR Drop outs: 0	confident not UIP. A confident diagnosis of UIP was made if all the ATS/ERS criteria were fulfilled: patchy involvement with clear evidence of chronic scarring/honeycombing and the presence of fibroblast foci in the absence of features against the diagnosis of UIP, such as granulomas and etc. A confident diagnosis of ‘‘not UIP’’ was made if there were clear features of an alternative diagnosis, or if none of the ATS/ERS criteria for UIP were present. Diagnoses of ‘‘probable UIP’’ and ‘‘probably not UIP’’ were more subjective; most commonly the former represented cases of extensive honeycombing without good evidence of patchy involvement in the sample reviewed, and the	alternate diagnosis (suggestive of NSIP or indeterminate)		evaluated Notes: The inter-observer variation of the existence of predominant distribution and the overall impression of the findings was analyzed using the k statistic. Inter-observer agreement was classified as follows: poor (k 5 0–0.20), fair (k 5 0.21–0.40), moderate (k 5 0.41–0.60), good (k 5 0.61–0.80), excellent (k 5 0.81–1.00). Comparison between definite UIP and the other two CT categories of abnormality was made using univariable analysis

Study details	Population	Methods	Outcome measures	Effect size	Comments
		latter were cases in which the histology was more suggestive of an alternative diagnosis. Only the 112 cases interpreted by the second lung pathologist as definitely being UIP were considered acceptable for the study Thin-section CT scans of all patients were reviewed in a random order by four radiologists All radiologists were informed about pathological and clinical UIP diagnosis. The radiologist evaluated the presence, extent, and distribution of CT findings and radiologic abnormalities, excluding emphysema, that were present in both lungs to determine the percentage of lung parenchyma occupied by the disease. After review of the			

Study details	Population	Methods	Outcome measures	Effect size	Comments
		findings, the CT scans in each case were classified by consensus as follows: definite UIP, consistent with UIP, suggestive of alternative diagnosis. The CT scan was classified as showing a definite UIP pattern when it demonstrated honeycombing in a predominantly peripheral and basal distribution. The CT was classified as consistent with UIP when it demonstrated a reticular pattern in a predominantly peripheral and basal distribution but only minimal or no honeycombing. The CT was classified as suggestive of alternative diagnosis when alternatives to UIP, such as NSIP, were more appropriate.			

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 41: Sverzellati 2010[459]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Sverzellati 2010 [459] Country of study: Italy & UK Study design: Retrospective Who was blinded: Reviewers Setting: NR Aim: document the spectrum of misleading thin-section CT diagnoses in people with biopsy-	Patient group: Patients on the interstitial lung disease databases of two teaching hospitals (Royal Brompton Hospital (London, England) and Morgagni Hospital (Forlì Italy)) between Jan 1, 2003, and Dec 31, 2006 Inclusion criteria: NR Exclusion criteria: coexistent infection cardiac failure acute exacerbation of disease at the time of CT All patients (core group) N: 55 Age (mean±SD): 59±6.2 Drop outs: 0	The core study group comprised consecutive patients who had a combined clinical-radiologic and pathologic diagnosis of IPF (biopsy proven) (n=55) Histological Evaluation Cases were reviewed by paired pathologists, and the diagnosis was confirmed according to accepted histopathologic criteria of UIP. To ensure that observers participating in this study assessed the thin-section CT appearance of the cases in the core study group in a blinded fashion, two other cohorts of people with chronic ILD were selected randomly from the ILD databases and mixed with the core study group. These cohorts comprised people with IPF diagnosed on the basis of clinical and thin-section CT criteria	Individual observations Rated as high probability IPF by radiologists	Observer 1:20/55 Observer 2:13/55 Observer 3:9/55	Funding: NR Limitations: Small sample size Study design-retrospective more prone to bias Notes: UIP was diagnosed histologically given the presence of temporal heterogeneity with non uniform and variable interstitial changes, including intermingled zones of established interstitial fibrosis, inflammation, fibroblastic foci, honeycomb change, and normal lung coexisting in variable proportions The diagnosis in people with mixed chronic and fibrotic cases was established at each
			Individual observations Rated as intermediate probability IPF by radiologists	Observer 1: 18/55 Observer 2: 7/55 Observer 3: 4/55	
			Individual observations Rated as low probability IPF by radiologists	Observer 1: 28/55 Observer 2: 38/55 Observer 3: 28/55	
			Number of patients given no differential diagnosis (with low probability of IPF diagnosis)	Observer 1: 21/28 Observer 2: 28/38 Observer 3: 19/28	
			Combined observations of IPF probability by 3 radiologists	High: 15/55 Intermediate: 6/55 Low: 34/55	
			Inter-observer	People with biopsy proven IPF =	

Study details	Population	Methods	Outcome measures	Effect size	Comments
proved IPF		(n=20) & a mixed group of subjects with various chronic and fibrotic interstitial lung diseases (n=48) In the mixed group, subjects had diseases such as NSIP (n = 17), sarcoidosis (n = 6), chronic hypersensitivity pneumonitis (HP (n = 8)), desquamative interstitial pneumonia (n = 5), fibrotic Langerhans cell histiocytosis (n = 4), organizing pneumonia (n = 3), mixed NSIP and organizing pneumonia (n = 3), and lymphoid interstitial pneumonia (n = 2). Clinical data (eg, absence of previous environmental exposures and connective tissue disease) were reviewed by two chest physicians Lung biopsy specimens with a histologic diagnosis of UIP were reviewed by paired pathologists Decisions were made with	agreement of first choice diagnosis	Moderate: (k = 0.45 (95% CI: 0.32, 0.58)) Whole study population= Fair: (k = 0.39 (95% CI: 0.34, 0.44))	participating institution on the basis of compatible clinical and histologic findings obtained by means of surgical lung biopsy (for HP, NSIP, organizing pneumonia, desquamative interstitial pneumonia, and lymphoid interstitial pneumonia) or transbronchial biopsy (for sarcoidosis). Unadjusted k coefficients of agreement were computed for the first-choice diagnosis in the entire study population and in the cohort of people with biopsy proved IPF. The weighted k (k w) coefficient of agreement was used to calculate the observer variation for the estimation of the probability of IPF diagnosis in the entire cohort and in the cohort of people with biopsy-proved IPF between paired observers (n = 3). To do this, the percentage

Study details	Population	Methods	Outcome measures	Effect size	Comments
		consensus. UIP was diagnosed by using the ATS and ERS criteria. Image Evaluation Images were reviewed independently by three thoracic radiologists They did not provide any cases included in the study population, and had no knowledge of clinical findings or details of the patient population and were not aware of the purpose of the study. The observers were asked to list their differential diagnoses (with no limit to the number of possible diagnoses) and to assign likelihood to each diagnosis (to the nearest 5%, totalling 100%). Specific diagnostic criteria for ILDs were not provided, so the diagnoses were based on each observer's own experience and understanding of the current CT literature.			likelihood given to each diagnosis was assigned a grade of 0 to 4, representing clinically useful probabilities: grade 0, condition not included in the differential diagnosis; grade 1, unlikely (5%–25 %); grade 2, intermediate probability (30%–65%); grade 3, high probability (70%–95%); grade 4, definite (100%). Observer agreement was categorized according to k values as: Poor (less than 0.20) fair (0.21–0.40) moderate,(0.41–0.60) good (0.61–0.80) excellent (0.81–1.00)

Study details	Population	Methods	Outcome measures	Effect size	Comments
		However, the observers used the terminology of the ATS and ERS classification for the diagnosis of idiopathic interstitial pneumonias.			

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

Table 42: Thomeer 2008 [470]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Thomeer 2008 [470] Country of study: 6 European countries (IFIGENIA RCT) Study design: Retrospective review Who was blinded:	Patient group: All of the patients included in the Idiopathic Pulmonary Fibrosis International Group Exploring N-Acetylcysteine I Annual (IFIGENIA) trial. All patients diagnosed with IPF by a specialist respiratory physician Inclusion criteria: Diagnosis of IPF was based on the international consensus criteria Aged 18–75 yrs. Newly diagnosed (<6 months) as well as previously diagnosed (>6 months) patients	Review by the radiological committee: The copies of the HRCT scans were reviewed independently by 3 members of the radiology committee, without knowledge of clinical, physiological or pathological parameters. Each member of the committee confirmed the diagnosis of UIP on thoracic HRCT based on the criteria of the international consensus statement.	Diagnosis of IPF by HRCT	Present: 165 (92.7%) Absent: 14 (7.3%)	Funding: NR Limitations: none Additional outcomes: Diagnosis of IPF by HRCT and/or biopsy for subgroups of patients (grouped by recruiting country) Inter-observer agreement between histology reviewers sub grouped by presence UIP in HRCT and % predicted FVC Inter-observer agreement between radiology
			Diagnosis of IPF by OLB/TLB	Present: 68 (84.0%) Absent: 14 (16.0%)	
			Definite diagnosis of IPF*	Present: 156 (87.2%) Absent: 23 (12.8%)	
			Inter-observer agreement between reviewers (mean weighted kappa coefficients)	HRCT reviewers: 0.33-0.46 ((0.23-0.36)-(0.44-0.56)) (95% CIs) Histology reviewers: 0.30 (0.12–0.48)	

Reviewers Setting: NR Aim: evaluate the diagnostic accuracy of respiratory physicians in IPF, and to calculate the interobserver agreement between HRCT reviewers and histology reviewers in the diagnosis of UIP	Exclusion criteria: NR All patients N: Age (mean±SD): Drop outs: NR	The degree of confidence in the diagnosis was recorded in terms of the scan being very suggestive, probable or unlikely for the diagnosis. The UIP diagnosis on thoracic HRCT was confirmed if the scan was scored as very suggestive or probable for UIP, and rejected if it was scored as unlikely. If disagreement occurred between the three members of the radiology committee, the UIP diagnosis agreed by the majority of the three members was accepted as definite. Review by the histology committee: The diagnosis of UIP according to the criteria of the ATS/ERS consensus classification was assessed by an independent panel of three pathology experts. The slides were reviewed independently without knowledge of clinical or			reviewers sub grouped by presence UIP in biopsy and no biopsy and % predicted FVC Notes: *defined as agreement of the histology and radiology committees with the diagnosis of IPF based on OLB/TLB and thoracic HRCT, or of the radiology committee when only HRCT scans were available. Weighted kappa coefficients (kw) were used to measure the level of inter-observer agreement. The kw were calculated using a method recommended for comparing level of agreement with categorical data along with their respective 95% CI

		physiological parameters. All slides were graded as being very suggestive, probable or unlikely for the diagnosis of UIP. For each observer, the UIP diagnosis on lung biopsy was confirmed if the slide was scored as very suggestive or probable for UIP and rejected if it was scored as unlikely. If the two reviewers disagreed as to diagnosis of UIP, the slides were sent to the third member of the pathology committee and assessed in an identical fashion. The diagnosis agreed by the majority of the three members was accepted as final. The diagnosis of UIP was rejected when one or both committees did not confirm a diagnosis of UIP.			

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test RBILD/ DIP= respiratory bronchiolitis interstitial lung disease/ desquamative interstitial pneumonia, UIP= usual interstitial pneumonia, NSIP= non-specific interstitial pneumonia

F.2 Prognosis

F.2.1 Serial pulmonary function tests

Table 43: DuBois2013[118]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Study: DuBois2013[1][18] Setting: Phase 3 clinical trial Duration of follow-up: 1 year Design: prospective	Patient group: IPF. All randomised subjects in a placebo-controlled Phase 3 clinical trial of interferon-gamma 1b irrespective of treatment assignment Inclusion criteria: All subjects who participated in the week-24 trial visit Confident IPF diagnosis according to ATS criteria FVC ≥55% predicted DLCO ≥35% predicted Either FVC or DLCO ≤90% predicted 6MWD≥150 metres Exclusion criteria: Subjects who died or had a lung transplant between the baseline and the week-24 visit, or who were lost to follow-up during this period.	All patients Followed up at 24 and 72 weeks Analysis Multivariable Cox proportional hazards model Subjects who were lost to follow-up or underwent lung transplant before the end of the second one-year follow-up period, or who survived through the end of the second one-year follow-up period were censored on the corresponding date. In analyses of IPF-related mortality, non-IPF related deaths were treated as competing events.	All cause mortality (over a 48-week period, N=79): Percent predicted FVC at baseline	</=50% vs. >/=80%: HR: 6.86 (95% CI:1.99-23.60), p value <0.01 51% - 65% vs. >/=80%: HR: 2.92 (95% CI: 1.39-6.13), p value <0.01 66%-79% vs. >/=80%: HR: 2.17 (95% CI:1.02-4.63), p value 0.05	Funding: NR Limitations: IPF-related mortality and all cause mortality presented separately Additional outcomes: Mortality according to change in baseline FVC, 24-change in FVC, baseline 6MWD, 24 week change in 6MWD. Mortality and IPF-related mortality according to respiratory hospitalisations. Notes: We assume that confounding factors adjusted for were: age, respiratory hospitalisations, baseline
			All cause mortality: 24-week change in percent-predicted FVC	</=10% vs. >-5%: HR: 5.86 (95% CI:3.33-10.31), p value <0.01 -5% - -9.9% vs. >-5%: HR: 2.74 (95% CI: 1.61-4.68), p value <0.01	

	All patients N=748 participated in the week-24 trial visit, and thus qualified for inclusion in the study population. Among the 748 subjects, 408 participated in the week 72 visit and thus the study database included a total of 1156 subject visits.		All cause mortality: Baseline 6MWD	<250m vs. >/=350m: HR: 2.12 (95% CI: 1.15-3.92), p value = 0.02 250-349m vs. >/=350m: HR: 1.28 (95% CI: 0.74-2.21), p value = 0.38	FVC, change in FVC, baseline 6MWD, change in 6MWD.
			All cause mortality: 24-week change in 6MWD	<-50m vs. >/=-25m: HR: 2.73 (95% CI: 1.60-4.66), p value <0.01 -50 to -26m vs. >/=-25m: HR: 2.94 (95% CI: 1.56-5.53) p value <0.01	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.

Table 44: Caminati 2009 [53]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Caminati 2009 [53] Country of	Patient group: Patients diagnosed with IPF (clinical-radiological or histological) according to ATS	All patients All patients underwent PFTs and gas exchange evaluations, according to	Baseline 6MWD Multivariable analysis for mortality	HR: 0.995 95% CI: 0.990-0.999 p value: 0.0308	Funding: NR Limitations: Age and sex adjusted for

study: Italy Study design: Retrospective cohort Who was blinded: NA Setting: NR Duration of follow-up: Mean 19.8 months (range 3.2-46.4)	criteria that underwent a 6 minute walk test on room air. Inclusion criteria: NR Exclusion criteria: Underlying connective tissue disease Exposure to environmental agents or drugs known to cause pulmonary fibrosis Underlying disorder known to cause pulmonary fibrosis If resting saturation was less then 90% on room air, patients were not considered eligible for 6MWT All patients N: 44 Age (mean): 61.9±1.5 M/F: 23/21 Drop outs: Unclear	ATS criteria, at baseline and 6 months. 6MWT: Patients walked on level ground using standardized instructions. The test was symptom limited and was stopped for safety purposes if the arterial oxygen saturation dropped to <86% Clinical data and survival data were obtained from medical records Analysis: Univariable Cox proportional hazard model was used to analyse the relationship between 6MWT and mortality (results not reported). Multivariate Cox proportional hazards model was used for each parameter adjusting for covariables, age and sex.	Oxygen saturation at rest Multivariable analysis for mortality	HR: 0.816 95% CI: 0.537-1.241 P value: 0.3416	in analysis, no other confounding factors considered Additional outcomes: The paper reports the correlation between physiologic and 6MWT parameters multivariable analysis of physiologic and 6MWT parameters associated with mortality Notes: 35 patients received drug therapy during the study period. During the follow-up period, 11/44 patients died for causes related to disease. 3 patients fulfil criteria for acute exacerbation of disease.
			Baseline FVC Multivariable analysis for mortality	HR: 0.365 95% CI: 0.124-1.078 p value: 0.0681	
			Baseline DLCO Multivariable analysis for mortality	HR: 0.723 95% CI: 0.548-0.954 p value: 0.0219	
			Change in 6MWD at 12 months Multivariable analysis for mortality	HR: 0.994 95% CI: 0.988-1 P value: 0.05	
			Change in oxygen saturation at rest, at 12 months Multivariable analysis for mortality	HR: 0.25 95% CI: 0.075-0.837 P value: 0.02	
			Change in FVC at 12 months Multivariable analysis for mortality	HR: 0.142 95% CI: 0.018-1.1 P value: 0.06	
			Change in DLCO at 12 months Multivariable	HR: 0.49 95% CI: 0.232-1.036 P value: 0.06	

			analysis for mortality		

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 45: DuBois 2011[121]

Study details	Population	Methods	Outcome measures	Effect size	Comments
DuBois 2011[121] Country of study: UK and USA Study design: Cohort from an RCT Who was blinded: N/A Setting: Unclear Duration of follow-up: 1 year	Patient group: All randomised patients in two placebo controlled clinical trials. Inclusion criteria: Patients required to have HRCT scan showing features consistent with protocol-defined criteria for either definite or probable diagnosis of IPF. Surgical lung biopsy was required to confirm suspected diagnosis in all patients with a clinical and radiographic diagnosis of probable IPF and all patients <50yrs. Exclusion criteria: NR All patients N: 1099 Drop outs: loss to follow-up n=18, deaths or lung transplant	All patients 24 week absolute change in percent – predicted FVC </= - 10%, - 5% to - 9%, > - 5% Change in percent-predicted FVC </= 50%, 51%-65%, 66%-79%, >/=80% Analysis: Change in percent-predicted FVC using Cox proportional hazards model. Change in percent predicted FVC was evaluated over the 24week periods. Confounding factors	24 week absolute change percentage predicted FVC </=-10% vs. >-5%:	HR:7.99 (95% CI: 5.26-12.14), p value: <0.001	Funding: Intermune Limitations: Inclusion of patients with mild to moderate IPF at baseline. Patients with severe IPF and emphysema were excluded. Notes: N patient visits = 1854 N deaths = 142
			24 week absolute change percentage predicted FVC 5 to -9.9% vs. >-5%	HR:2.60 (95% CI: 1.75-3.85), p value: <0.001	
			24 week absolute change percentage predicted FVC >-5% predicted	Reference : 1.0	
			change percentage predicted FVC </=50% predicted	</=50% vs. >/=80%: HR: 5.79 (95% CI:2.55-13.15), p value <0.001	
			change percentage predicted FVC 51 to 65	51% - 65% vs. >/=80%: HR: 3.54 (95% CI: 1.95-6.44), p value <0.001	

	n=39 M/F: 70.2% male Age, yrs: <60 – 21.8% 60-69 – 43.1% >/= 70 – 35.1%	adjusted for: age, oxygen use, surgical lung biopsy, history of respiratory hospitalisation, drug treatment, physiologic % predicted FVC, 24 week change in % predicted FVC, % predicted DLCO, 24 week change in % predicted DLCO, dyspnoea and HRQL UCSD SOBQ and 24 week change in UCSD SOBQ.	change percentage predicted FVC 66 to 79	66%-79% vs. >/=80%: HR: 2.20 (95% CI:1.19-4.09), p value 0.012	
			change percentage predicted FVC >/= 80	Reference : 1.0	

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 46: DuBois 2011[121]

Study details	Population	Methods	Outcome measures	Effect size	Comments
DuBois 2011[121] Country of study: Multi national Study design: Cohort from an RCT Who was	Patient group: All randomised patients in two placebo controlled clinical trials. (All patients: N=1156, Drop outs: Not reported, M/F: 812/344, Age: mean 65.3 (8.1SD), Group 1: IFN-gamma 1b –n=713, Group 2: Placebo – n=443) Inclusion criteria: Patients required to have HRCT scan showing features consistent with protocol-defined criteria	All patients 24 week absolute change in percent – predicted FVC </= - 10%, - 5% to - 9%, > - 5% Change in percent-predicted FVC </= 50%, 51%-65%, 66%-79%, >/=80% Analysis: Change in percent-	24 week absolute change percentage predicted FVC </=-10% vs. >-5%	Patient visits (n):166 Deaths (n):39 1 year risk of death: HR:4.78 (95% CI: 3.12-7.33) p value: <0.001	Funding: Intermune Limitations: Patients selected from 1156 patients recruited in two clinical trials. Patients receiving active drug treatment during were adjusted for in the analysis, but adjusting of other confounders such as, age, sex, baseline PFTs, smoking status and
			24 week absolute change percentage predicted FVC -5 to -10% vs. >-5%	Patient visits (n):373 Deaths (n):45 1 year risk of death: HR:2.14 (95% CI: 1.43-3.20) p value: <0.001	
			24 week absolute	Patient visits (n):1316	

blinded: N/A Setting: Unclear Duration of follow-up: 1 year	for either definite or probable diagnosis of IPF. Surgical lung biopsy was required to confirm suspected diagnosis in all patients with a clinical and radiographic diagnosis of probable IPF and all patients <50yrs. Exclusion criteria: NR All patients N: 1156 Drop outs: Not reported M/F: 812/ 344 (70.2%/ 29.8%) Age (mean, SD): 65.3 years (8.1)	predicted FVC taken at week 24 and 1 year risk using Cox proportional hazards model. Change in percent predicted FVC was evaluated over the 24week periods immediately preceding the week 24 and week 72 trial visits, respectively and defined categorically based on prior research.	change percentage predicted FVC >-5% predicted	Deaths (n):56 Reference : 1.0	previous hospitalisations, not reported. Notes: Authors report that all deaths occurring over 48weeks of the trail were included in the analysis; subjects who were lost to follow-up and those who underwent lung transplant during follow-up were censored on the corresponding date.
			change percentage predicted FVC </=50% predicted	Patient visits (n):203 Deaths (n):42 1 year risk of death: HR:7.44 (95% CI: 3.28-16.87) p value: <0.001	
			change percentage predicted FVC 51 to 65	Patient visits (n):691 Deaths (n):65 1 year risk of death: HR:4.09 (95% CI: 1.87-8.98) p value: <0.001	
			change percentage predicted FVC 66 to 79	Patient visits (n):594 Deaths (n):26 1 year risk of death: HR: 1.97 (95% CI: 1.87-8.98) p value: 0.111	
			change percentage predicted FVC >/= 80	Patient visits (n):374 Deaths (n):7	

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 47: Hallstrand 2005[172]

Study	Population	Methods	Outcome measures	Effect size	Comments

details					
Hallstrand 2005[172] Country of study: USA Study design: Prospective cohort Who was blinded: NR Setting: the Interstitial Lung Disease Clinic, University of Washington Medical Center, Seattle, WA, USA, and for further evaluation	Patient group: Consecutive new referrals for further management of IPF. Patients with IPF who were entered into this study had progressive symptomatic and/or physiological deterioration, despite treatment with prednisone with or without immunosuppressives. Inclusion criteria: Consented to the study met the diagnostic criteria for IPF* Exclusion criteria: Collagen vascular disease, occupational lung disease, sarcoid, hypersensitivity pneumonitis and other idiopathic interstitial pneumonias Patients with concurrent emphysema were excluded based on elevated residual volume of ≥120% and (FEV1)/ (FVC) ratio of f 0.60. All patients	All patients: Timed walk test (TWT): TWT on a 30-m-long level course. Patients walked at a pace comfortable to them until they became too fatigued, up to a maximum of 6 min** The test was stopped when saturation reached 80%, the lowest saturation was recorded if the saturation continued to decline. FVC and DLCO were performed were performed within 24 hours of the TWT according to ATS criteria. Analysis: Survival time was measured in days from enrolment until death or censoring (patients censored at the end of the follow-up period or if patients underwent lung transplantation). Multivariable Cox	Multivariable analysis Walk distance 30-m units to mortality	Relative hazard (95% CI): 0.91 (0.81–1.02) P value: 0.098	Funding: NR Limitations: Baseline characteristics for each group not reported Effect could be due to confounding Selection bias Unclear cut-off for distance walked Additional outcomes: Effect of supplementary oxygen on walk distance, velocity and saturation Association of the timed walk test with pulmonary function Notes: *The diagnosis of IPF was ascertained by typical clinical, radiographical, non-diagnostic transbronchial biopsy, and physiological features consistent with IPF; surgical lung biopsy demonstrating histological features of usual interstitial
			Multivariable analysis Resting room air arterial oxygen saturation to mortality	Relative hazard (95% CI): 1.06(0.83–1.37) P value: 0.637	
			Multivariable analysis DLCO % pred to mortality	Relative hazard (95% CI): 0.92(0.87–0.98) P value: 0.005	
			Multivariable analysis FVC % pred to mortality	Relative hazard (95% CI): 0.94(0.97–1.02) P value: 0.646	

and management in the Interstitial Lung Disease/Sarcoid/Pulmonary Fibrosis Program at the University of Washington Duration of follow-up: Median (range) 5.4 years (4.3-6.2)	N: 28 Drop outs: 5 (underwent lung transplantation) Age (mean): 62.7(57-69) M/F: 19/9 Smokers: 19 (67.9%)	proportional hazards models were adjusted for age, sex, FVC % pred, time from the onset of symptoms and supplemental oxygen administration during the test.			pneumonia was accepted for the diagnosis of IPF in patients not meeting the major and minor clinical criteria. ** Patients with resting room air saturation of 88% had TWT in room air and with 2 L of oxygen. Patients with resting saturation ≤88% were tested only on 2 L of oxygen. The test was stopped for safety if the patient had signs of overt fatigue and/or asked to stop, or the saturation dropped to <80%. Survival time was measured in days from enrolment until death or censoring. Patients were censored at the end of the follow-up period or if they underwent lung transplantation 19 out of 28 (67.9%) patients died within 2 yrs from the time of the

					baseline TWT, 22 out of 28 (78.6%) died over the entire follow-up period at an average (range) of 1.2 yrs (0.2–3.0) from enrolment. During the study period, five patients underwent single-lung transplant at an average of 1.5 yrs (1.0–2.4) from enrolment and were censored in the analysis at the time of transplantation. Disease severity ranged from FVC ≥70% predicted in eight patients and ≤40% predicted in five. All patients had progressive disease based on symptoms or pulmonary function tests, despite treatment with prednisone with or without Azathioprine.

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 48: Hamada2007 [173]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Hamada2007 [173] Country of study: Japan Study design: Prospective cohort Who was blinded: NR Setting: University hospital Duration of follow-up: 5 years	Patient group: Patients with IPF diagnosed by pathology, "none of whom were receiving corticosteroids or immunosuppressive agents at the time of workup". Inclusion criteria: As above Exclusion criteria: Patients who died within a month of open lung biopsy, had collagen vascular diseases, asbestosis, venoocculusive disease with Langerhans cell histocytosis. Other disorders that could cause secondary PAH were excluded, including pulmonary arterial thromboembolism, connective tissue disease, chronic liver dieases and obstructive sleep apnea syndrome. All patients N: 78	All patients Right hearted catherisation and PFTs were performed in the same week in most patients. No further details on measurements reported. Analysis Survival rates estimated using Kaplan-Meier nonparametric survival model. Regression analysis performed to evaluate factors contributing to survival: age, gender, mean pulmonary arterial pressure, Pa02, P02 in mixed venous blood, FVC % predicted, DLCO% predicted and cardiac index.	Preserved DLCO (%DLCO>/=40%, n=27)	19/27 (70.4%) survived for 5 years compared to low DLCO group (p value<0.001)	Funding: NR Limitations: Small sample analysed. Notes: Study objectives were to evaluate long term clinical course of patients with IPF complicated with pulmonary arterial hypertension
			Low DLCO (<40, n=25)	5/25 (20%) survived for 5 years RR2.70 (95% CI: 1.46 to 4.99) p value < 0.001	
			Causes of death	Respiratory failure due to IPF: 33/52 Pulmonary infection: 1 Lung cancer: 9 Other malignancies: 3 Cardiac disorders: 4 Cerebrovascular disorders: 1 Unknown: 1	

	Age (mean): 62+/-8 years Drop outs: unclear M/F: 53/8				

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 49: Jeon 2006[219]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Jeon 2006[219] Country of study: South Korea Study design: Retrospective cohort Who was blinded: Not reported Setting: Hospital Duration of follow-up: >1 year (unclear)	Patient group: Patients pathologically confirmed to have UIP on surgical lung biopsy and patients diagnosed as IPF positive by diagnostic American Thoracic Society criteria Inclusion criteria: As above Exclusion criteria: Clinical evidence of connective tissue disease, occupational or environmental exposure, or a history of ingestion of a drug known to cause ILD All patients N: 88 Drop outs: Not reported Age: 60.3 mean (+/-7.5 SD)) M:F – 69:19	All patients FVC and DLCO as continuous variables PFTs were obtained within 2 weeks at the time of diagnosis and measured as recommended by ATS criteria. Analysis: Patients grouped according to whether they were managed by pharmacological treatment or symptomatic supportive care only. Cox proportional hazards regression was used to identify	Baseline PFTs (mean+/-SD %predicted): FVC: 74.0 +/- 19.2 DLCO: 65.2 +/- 21.4	FVC Specific treatment group: 74.6 +/- 18.1 Symptomatic supportive care: 73.2 +/- 20.8 p value: 0.758 DLCO Specific treatment group: 64.7 +/- 20.5 Symptomatic supportive care: 65.8 +/- 22.9 p value: 0.834	Funding: NR Limitations: Patients with UIP and IPF grouped together in analysis Predictors of mortality for patients with IPF by multivariable analysis not presented by treatment group compared to supportive care group. Adjusted for age, sex, severity of dyspnoea, FVC and DLCO and treatment, multivariable survival analysis.
			Predictors of mortality of IPF patients by multivariable analysis (% predicted)	FVC HR: 1.7 (95% CI: 1.2-2.3) p value: 0.004 DLCO HR: 1.5 (95% CI: 1.1-2.1) p value: 0.033	
			Causes of death in	Respiratory failure 34 (68%)	

	Group 1: Specific treatment group N: 49 Age (mean): 58.9 (+/-7.1 SD) Drop outs: Not reported Group 2: Symptomatic supportive care N: 39 Age (mean): 62.1 (+/-7.8 SD) Drop outs: Not reported	variables associated with survival rate. Hazard ratios were reported for these analyses.	patients with IPF (n=50)	Acute exacerbation 23 Slow progression 11 Infection 7 (14%) HAP 4 CAP 2 Wound infection 1 Lung cancer 4 (8%) Pulmonary embolism 1 (2%) Cardiovascular disease 1 (2%) Variceal bleeding 1 (2%) Unknown 2 (4%)	

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 50: Kurashima 2010 [260]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Kurashima 2010 [260] Country of study: Japan Study design: Retrospective cohort Who was	Patient group: Patients previously diagnosed with UIP based on HRCT findings, with or without emphysema. Inclusion criteria: Medical records, PFT results and laboratory tests reviewed and patients selected according to following criteria: patients who underwent HRCT for clinical symptoms or other medical reasons and who were	All patients FVC and DLCO as continuous variables PFTs performed according to the ATS criteria. Analysis: Survival analysis was performed by the Kaplan Meier method, with end points being death or censoring of data. A univariable Cox's	Baseline characteristics in patients with UIP	%FVC (n=348): 71.8 +/- 19.4 %DLCO (n=202): 74.3 +/- 20.1	Funding: NR Limitations: Confounding factors adjusted for in multivariable survival analysis were emphysema, FVC % predicted, FEV/FVC per 1% and DLCO% predicted. Patients receiving treatment were not adjusted for in analysis
			Multivariable Cox's proportional hazards regression model for risk of death in patients with UIP	%FVC predicted per 1% (n=362) HR:0.988 (95% CI: 0.967-1.010) p value: 0.27 %DLCO predicted per 1% (n=251): HR: 0.987 (95%CI: 0.971-1.002) p value: 0.21	
			Causes of death in patients with UIP	Lung cancer 8 (12.1%) Acute exacerbation 21 (31.8%)	

blinded: Thoracic radiologists blinded to clinical details Setting: Hospital Duration of follow-up: 0	diagnosed with UIP by radiologists. Exclusion criteria: Connective tissue disease, diagnosis of other ILD, such as drug-induced ILD. Patients without PFT results and patient with lung cancer were excluded from analysis of PFT and HRCT findings and from survival analysis All patients N: 660 (UIP, n=439: UIP with emphysema, n=221) Drop outs: Unclear M/F: 336/103 Age: 72.9 years +/-8.1 Patients receiving treatment: n=8	proportional hazards regression model followed by multivariable analysis was used to identify risk factors for mortality.		Chronic Respiratory failure 26 (39.4%) Other causes 11 (16.6%)	Notes: Total of 1050 patients with possible diagnosis of UIP on HRCT were screened. For 660 patients (UIP with and without emphysema) the diagnostic findings were compatible with IPF. Of these 238 patients had lung cancer at diagnosis and PFT results were not available for 131 patients.

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 51: Lynch 2005 [292]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Lynch 2005 [292]	Patient group: mild to moderate IPF	HRCT features	Overall extent of fibrosis score-multivariable analysis	Hazard ratio (calculated by the Cox proportional hazards model, stratifying by smoking status): 2.71	Funding: InterMune

Country of study: multi-national (United states, Europe, Canada and South Africa) Study design: (e.g. RCT) patients from an RCT Who was blinded: (if RCT) N/A Setting: 58 medical centres (39 academic, 19 community based) in the USA, Europe, Canada and South Africa	Inclusion criteria: as above Exclusion criteria: NR All patients: N: 315 Age (mean): NR Drop outs: unclear	Baseline FVC and DLCO results presented, but no details provided on these measurements. Analysis: Stepwise logistic regression (stratified by smoking status) model built using variables with a univariable p values <0.2. These were overall disease extent score on HRCT, reticulation pattern score, honeycomb pattern score, predominant pattern reticulation, A_a gradient and current O2 use.		95% confidence interval of hazard ratio: 1.61, 4.55 p value: <0.0001	Limitations: Possible bias from radiologists who knew patients were being entered into a trial of treatment for IPF Additional outcomes: Agreement on diagnosis between radiologists HRCT characteristics according to HRCT classified as consistent with, or not consistent with IPF Clinical features according to HRCT classified as consistent with, or not consistent with IPF Correlation between baseline HRCT and baseline clinical characteristics Notes: Patients were enrolled in a trial of Interferon
			Baseline % predicted DLCO – multivariable analysis	Hazard ratio: 0.94 95% confidence interval of hazard ratio: 0.90, 0.98 p value: 0.004	

Duration of follow-up: NR					

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 52: Manali 2008[300]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Manali 2008[300] Country of study: Greece Study design: Retrospective cohort Who was blinded: Not reported Setting: Respiratory outpatient clinic Duration of	Patient group: 25 consecutive patients with IPF recruited from respiratory outpatients clinic Inclusion criteria: All patients had IPF based on American Thoracic Society criteria and lung biopsies obtained by video assisted thoracoscopic surgery which showed UIP Exclusion criteria: Secondary causes of lung fibrosis: none of the patients had a history of environmental or occupational exposure, drug toxicity or connective tissue disease as documented by history, clinical and immunological tests. All patients N:25 Drop outs: 12/25 deaths	All patients: FVC as a continuous variables Lung function tests were measured during the diagnostic approach. Analysis: The patients still alive during the reporting of this study were censored for survival analysis (13/22.. Univariable and multivariable Cox regression analysis was conducted for survival.	Impact on survival using multivariable Cox regression analysis	FVC RR 1.045 (95% CI: 0.956-1.142) p value: 0.033	Funding: Thorax Foundation, Athens Limitations: Multivariable survival analysis adjusting for confounders not clearly reported Additional outcomes: Deaths 12/25

Study details	Population	Methods	Outcome measures	Effect size	Comments
follow-up: 0	Age: 64+/-2years M/F: 12/13				

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 53: Mejia 2009 [311]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Mejia 2009 [311] Country of study: Mexico Study design: Retrospective Cohort Who was blinded: (if RCT) N/A Setting: National	Patient group: IPF (2000 ATS/ERS criteria) Inclusion criteria: as above Exclusion criteria: Other ILDs. Atypical HRCT findings other than emphysema All patients N: 110 M/F: 72%/28% Age (mean): 64±9.5 years Drop outs: NR Patients with IPF alone N= 79 M/f: 49/30	Estimated systolic pulmonary artery pressure (eSPAP). Pulmonary artery hypertension (PAH) was defined by an eSPAP ≥45mmHg. Baseline PAH eSPAP >50mmHg: IPF alone: 39/68; IPF+ emphysema: 26/29 eSPAP>75mmHg: IPF alone: 8/68; IPF+ emphysema: 21/29 HRCT scan fibrotic score FVC <50% predicted	Mortality (multivariable analysis) Mortality (multivariable analysis)	eSPAP >75mmHg: HR 2.25 95% CI 1.12-4.54 p value 0.022 FVC<50% predicted: HR 2.6 95% CI 1.19-5.68 p value 0.016	Funding: Universidad Nacional Autonoma de Mexico Limitations: Not all data reported- prognosis for subgroups defined at baseline not reported Small study Retrospective Analysis performed on whole group which included co-existing emphysema which could have confounded the results

Institute of Respiratory Diseases, Mexico Duration of follow-up: NR	Age, year: 63±10 Smoking status: Yes: 36 No: 40 Pack years: 0 (0-78). Subgroup: Patients with IPF and Emphysema N= 31 M/f: 30/1 Age, year: 67±7 Smoking status: Yes: 24 No: 7 Pack years: 5 (0-60)				Additional outcomes: Univariable analysis for male gender Notes: Multivariable analysis performed with the variables showing influence on mortality as identified with univariable analysis

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 54: Mogulkoc 2001A [327]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Mogulkoc 2001A [327] Country of study: UK Study design: cohort	Patient group: mild to moderate IPF; age <65 years; potentially eligible for lung transplantation Inclusion criteria: as above Exclusion criteria: (1) the presence of known histories of collagen vascular disease, allergic	DLCO HRCT score, n (%) HRCT fibrosis score: 2.1±0.7 HRCT ground glass score: 3.0±1.3	HRCT fibrosis score at baseline- multivariable analysis (n=85)	HRCT fibrosis score- baseline HR/ OR: 2.067 95% CI: 1.726- 3.914 p value: 0.026	Funding: NR Limitations: patients were all <65 years Additional outcomes: Survival probability according to method of diagnosis
			DLCO % predicted at baseline (n=85)	HR/ OR: 0.957 95% CI: 0.928- 0.987 p value: 0.005	
			DLCO % predicted at 2 year follow-up (n=70)	HR/ OR: 0.923	

Who was blinded: (if RCT) Setting: North West Lung Research Centre, UK Duration of follow-up: 26.2 months (median), range 1-97 months	alveolitis, or exposure to organic dusts; (2) patients with a tissue diagnosis of nonspecific interstitial pneumonia (NSIP)/fibrosis, desquamative interstitial pneumonia (DIP), respiratory bronchiolitis associated with interstitial lung disease (RB-ILD), or bronchiolitis obliterans organizing pneumonia (BOOP); (3) patients with a predominantly ground-glass attenuation on HRCT scan (16, 17); (4) patients who demonstrated an objective response to corticosteroids alone; (5) patients who subsequently underwent lung transplantation; (6) patients older than 65 yr were excluded (on the grounds that they are not eligible for transplantation). All patients N: 115 Age (mean): 56±8 years M/F: 81/34 Drop outs: 20			95% CI: 0.863- 0.988 p value: 0.021	Notes: Potential lung transplant patients All patients had been treated with corticosteroids and various chemotherapeutic regimes before and after referral to the centre. Cox regression and logistic regression used Variables that were significant by univariable Cox regression analysis were taken as potential predictors of survival and were then used as covariates in multivariable analysis..

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 55: Mura 2012[333]

Study	Population	Methods	Outcome measures	Effect size	Comments

details					
Mura 2012[333] Setting: Pulmonary unit, Italy 2005-2007 Duration of follow-up: 3 years Design: prospective cohort	Patient group: Newly-diagnosed IPF n=70 Inclusion criteria: ATS 2000 guideline diagnosis of IPF VATS confirmed UIP Exclusion criteria: Collagen vascular disease, drug toxicities, domestic or professional environmental exposures. All patients (n=70) M/F: 57/13 Time to diagnosis (months): 23±20 Biopsy based diagnosis yes/no: 23/47 6MWD (m) (n=64): 372±146 6MWD (% pred.) (n=64) fVC (% pred): 75±22 DLCO (% pred): 46±19	All patients Had baseline evaluation including Medical Research Council Dyspnoea score, 6-min walk test, PFTs, all of which were repeated at 6 months. HRCT scans without histological confirmation were independently reviewed by 3 radiologists Analysis Cox proportional hazards regression analysis was used to identify significant variables predicting survival status. Variables selected via univariable analysis were evaluated in the multivariable Cox regression analysis. P values <0.05 were regarded as significant.	Acute exacerbations (Cox proportional hazard analysis of variable at time of diagnosis) DLCO % predicted	HR 0.93 (0.89- 0.97) P value 0.008	Funding: Scuole di Specializzazione in Malattie dell'Apparato Respiratario, Universita di Roma "Tor Vergata" and Universita degli Studi di Siena Limitations: Both 6MWD (m) and 6MWD (%predicted) were measured against an unknown threshold not used in the UK. Additional outcomes: Univariable analysis of variables linked with acute exacerbations. Multivariable analysis of concomitant emphysema on acute exacerbations. Comparative analysis in the retrospective cohort Mean survival from time of diagnosis was

					30 months 3 year mortality was 46% Mortality (Cox proportional hazard analysis of variable at time of diagnosis) 6MWD <72% predicted - HR 3.27 (1.25-8.82) P value 0.0162 Notes: 24 (34%) subjects had concomitant emphysema. Survival was defined as the time to death or lung transplant. Multivariable survival analysis adjusted for: BMI, MRC dyspnoea score, 6MWD, desaturation at 6MWD, PaO2, FV % predicted, DLCO % predicted, composite physiologic index, HRCT fibrosis score, BAL total cell counts and concomitant emphysema. A retrospective

					cohort of 68 patients was used for confirmation.

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.

Table 56: Richeldi 2012A[410]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Richeldi 2012A[410] Setting: Two independent longitudinal cohorts, USA Duration of follow-up: 12 months Design: cohort	Patient group: newly-diagnosed IPF (ATS 2000 guideline) Inclusion criteria: Two serial FVC measurements 12 months apart Exclusion criteria: NR All patients n=142 Age: 67 years (mean) Male: 74% History of smoking: 69% Biopsy proven disease: 56% FVC (L): 2.70 mean, SD 0.78 FVC, % predicted: 67.6 mean, SD 16.1	All patients Analysis Logistic regression was used to determine the association of dichotomised decline in FVC with 2 year transplant-free survival. Unadjusted analyses were performed, followed by adjustment for age, gender, O2 use and baseline % predicted FVC and DLCO (only adjusted results presented in this table)	Death or transplant (time to event) ≥10% decline in FVC (L) at 12 months (adjusted OR/HR)	OR/HR3.54 (2.04 to 6.15) no p value	Funding: NIH grant HL086516 Limitations: none Additional outcomes: Frequency of ≥5%, ≥10% and ≥15% decline in FVC at 12 months for whole cohort, and excluding patients with severe disease. Unadjusted OR/HRs for all death/ death or transplant outcomes Transplant-free survival at 2 years for 12 month FVC
			Death (time to event) ≥10% decline in FVC (L) at 12 months (adjusted OR/HR)	OR/HR2.78 (1.48 to 2.54) no p value	
			Death or transplant at 2 years (time to event) ≥5% decline in % predicted FVC at 12 months (adjusted OR/HR)	1.91 (1.12-3.26) relative change 3.24 (1.84-5.69) absolute change	
			Death at 2 years	1.61 (0.89-2.92) relative change	

			(time to event) ≥5% decline in % predicted FVC at 12 months (adjusted OR/HR)	2.89 (1.53-5.46) absolute change	declines of >5, >10 and >15% Notes: 19% of patients were on long-term oxygen therapy 35% current or previous prednisone use Multivariable analysis adjusted for age, gender, O2 use and baseline % predicted FVC and DLCO
			Death or transplant at 2 years (time to event) ≥10% decline in % predicted FVC at 12 months (adjusted OR/HR)	3.38 (1.93-5.90) relative change 3.27 (1.77-6.05) absolute change	
			Death at 2 years (time to event) ≥10% decline in % predicted FVC at 12 months (adjusted OR/HR)	2.75 (1.46-5.17) relative change 2.41 (1.15-5.05) absolute change	
			Death or transplant at 2 years (time to event) ≥15% decline in % predicted FVC at 12 months (adjusted OR/HR)	3.5 (1.94-6.31) relative change 2.44 (1.12-5.32) absolute change	
			Death at 2 years (time to event) ≥15% decline in % predicted FVC at 12 months (adjusted OR/HR)	3.18 (1.16-6.26) relative change 2.49 (1.02-6.06) absolute change	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity,

TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.

Table 57: Schmidt 2011 [424]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Schmidt 2011 [424] Country of study: USA Study design: Retrospective cohort Who was blinded: NR Setting: Secondary care Duration of follow-up: 5.2-6.6 years	Patient group: Patients with IPF were selected from the university of Michigan interstitial lung disease database. Diagnosis made with either surgical lung biopsy or HRCT scan diagnostic of UIP using standard criteria. Inclusion criteria: PFT performed within 3 months of diagnosis. Exclusion criteria: NR All patients: Baseline N: 321 Age: 63.9±9.7 Drop outs: 0 M/F:217/104 Ever tobacco use: 236 (73.5%) All patients: 6 months	All patients FVC and DLCO as continuous variables PFT measured at diagnosis and at least one PFT after baseline Analysis Longitudinal analysis: For 6 months; PFTs included from 3-9 months included in analysis. An estimated PFT value was obtained from regression For 12 months; PFTs included from 9-15 months after diagnosis Cox proportional hazard models used to evaluate changes in Composite	Longitudinal HR for mortality by absolute decrease in PFTs: % FVC predicted Over 6 months (n=211)	5%: HR 1.8(95% CI: 1.2-2.7), p value 0.002 10%: HR 1.4(95% CI: 0.9-2.1), p value 0.122 15%: HR 1.1(95% CI: 0.6-1.8), p value 0.857 20%: HR 2.0(95% CI: 1.0-4.0), p value 0.051	Funding: National institutes for health National heart, lung and blood institute Limitations: none Additional outcomes: Longitudinal hazard ratios for mortality associated with absolute increases in composite physiologic index (CPI) and relative decreases in individual PFTs over 6 and 12 months in patients with combined IPF and emphysema. Notes: Mortality data were confirmed through social security death registry index
			Longitudinal HR for mortality by absolute decrease in PFTs: % DLCO predicted Over 6 months (n=211)	10%:- HR 1.7(95% CI: 1.1-2.5), p value 0.011 15%: HR 1.6(95% CI: 1.1-2.5), p value 0.029 20%: HR 1.8(95% CI: 1.1-3.0), p value 0.030 25%: HR 2.3(95% CI: 1.2-4.2), p value 0.010	
			Longitudinal HR for mortality by absolute decrease in PFTs: % FVC predicted Over 12 months (n=144)	5%: HR 1.8(95% CI: 1.1-2.9), p value 0.012 10%: HR 2.4(95% CI: 1.5-3.8), p value <0.001 15%: HR 2.6(95% CI: 1.6-4.5), p value <0.001 20%: HR 3.6(95% CI: 1.9-6.9), p value <0.001	
			Longitudinal HR for mortality by absolute decrease in PFTs: % DLCO predicted	10%:- HR 2.2(95% CI: 1.4-3.5), p value 0.001 15%: HR 2.3(95% CI: 1.5-3.7), p value <0.001 20%: HR 3.0(95% CI: 1.8-4.9), p value <0.001	

	N: 211 Age (mean): 63.2±10 Drop outs: 0 M/F:151/60 Ever tobacco use: 162(76%) All patients: 12 months N: 144 Age (mean): 62.3±10 Drop outs: 0 M/F:102/42 Ever tobacco use: 109 (75.7%)	physiologic index and PFTs in patients stratified by amount of emphysema.	Over 12 months (n=144)	25%: HR 3.5(95% CI: 2.0-6.1), p value <0.001	censured by 3 months to account for reporting lag. Follow up time was determined from date of baseline PFT to date of death or censure

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 58: Zappala 2010[507]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Zappala 2010[507] Country of study: UK and Australia Study design: Retrospective Cohort	Patient group: January 1978-June 2005 patients who met the histological criteria at surgical biopsy for IPF. Inclusion criteria: ATS/ERS diagnostic criteria Exclusion criteria: Patients without serial PFT data All patients	Serial PFT trends at 6(±2)months expressed as percentages of baseline values, were evaluated for FVC (measured using spirometer) and DLCO (measured by single breath/re-breathing technique using respirometer) relative trends were defined a priori as significant (FVC	Progression free survival patients with 5-10% decline in FVC compared with stable disease	HR; 1.82 (0.97-3.40) P value; 0.06	Funding: NR Limitations: Additional outcomes: Study looked at patients with NSIP too but did some separate analysis for IPF patients (for which data has been extracted)
			Progression free survival patients with 5-10% decline in FVC compared with stable disease- adjusted for baseline DLCO	HR; 2.56 (1.17-4.38) P value; 0.02	

Setting: Secondary care Duration of follow-up: 6 months ±2	N: 84 (only IPF excluding NSIP) Age (mean): 57.4±8.50 Drop outs: 0 m/f: 69/15 smokers (n): ever/never: 62/22	> 10% predicted, DLCO > 15% predicted)or marginal (FVC 5-10% predicted; DLCO 7.5-15% predicted) compared with baseline. Criteria for marginal decline were chosen to allow rapid computation in clinical practice reflecting the rational of current ATS criteria for significant PFT change. PFT trends analysed using proportional hazards analysis and multivariable analysis adjusting for age, sex, smoking status and baseline disease severity			Notes: Transplanted patients n=4 were censored as alive at date of transplant Treatment regimes included combination immunosuppressant treatment including low dose prednisolone (10mg) or high dose prednisolone (40-60mg) initially reducing to maintenance average of 10mg * includes NSIP patients n=72 ** excluding patients with a significant decline in FVC HR; 2.34 (1.19-4.60) P value; 0.01 HR; 2.31 (1.19-4.50) P value; 0.014 HR;3.33 (1.61-6.88) P value; <0.001

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society*

F.2.2 Sub-maximal exercise tests

Some studies reported on more than one prognostic factor the information for sub-maximal exercise tests is in the following evidence tables located in the serial pulmonary function test subsection:

Table 43:

Table 44: Caminati 2009

Table 47: Hallstrand 2005

F.2.3 Echocardiography

Some studies reported on more than one prognostic factor the information for echocardiography is in the following evidence tables located in the serial pulmonary function test subsection:

Table 37: Mejia 2009 [311]

F.2.4 CT scores

Some studies reported on more than one prognostic factor the information for CT scores is in the following evidence tables located in the serial pulmonary function test subsection:

Table 35: Lynch 2005 [292]

Table 54: Mogulkoc 2001A

Table 59: Best 2008[38]

Study details	Population	Methods	Outcome measures	Effect size	Comments

Study details	Population	Methods	Outcome measures	Effect size	Comments
[38] Country of study: USA Study design: Retrospective cohort Who was blinded: N/A Setting: Hospital Duration of follow-up: 0.9-2.7 years (median follow-up, 1.5years)	Patient group: Patients enrolled in a clinical trial of interferon β-1a for treatment of IPF. (IPF diagnosed using American Thoracic Society criteria). Inclusion criteria: Progression of IPF, defined as meeting at least one of the following: >10% relative decrease in TLC or FVC or >15% relative decrease in DLCO >3% decrease in resting oxygen saturation level, a 3mm Hg increase in the resting gradient between the partial pressure of oxygen in the artery and that in the alveoli, or a 5% decrease in oxygen saturation with exercise Radiologic progression of disease as assessed on chest radiographs or thin-CT images Exclusion criteria: Environmental or drug exposures likely to cause ILD Connective tissue disease Emphysema occupying more than 50% of the lung End stage IPF defined as meeting at least two of the following: TLC less than 45% of predicted volume Haemoglobin-corrected DLCO <25% of predicted capacity	All patients: CT visual score: fibrosis (%), ground glass opacity (GGO) %, emphysema (%) Analysis: Survival analysis performed to assess value of each variable accounting for differences in duration of follow-up. Potential predictors were used in the Cox proportional hazards model for univariable analysis. No further details provided	Mortality prediction (multivariable logistic regression analysis)	Fibrosis OR estimate: 1.104 95% cI: 1.018, 1.198 P value: 0.017	Funding: NR Limitations: Outcome measures not clearly reported in paper. Paper reports that univariable analysis for treatment assignment conducted, but results unclear. Paper reports that univariable and multivariable logistic regression analysis was performed to predict mortality, however multivariable analysis data for FVC was not presented. Additional outcomes: Mortality: 35/167 (21.0%) Abstract reports that at multivariable analysis, FVC (P=0.006). This is not presented in the paper. No further details provided. Notes: N/A

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

Table 60: Sumikawa 2008[454]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Sumikawa 2008[454] Country of study: USA Study design: Retrospectiv ecohort Who was blinded: N/A Setting: unclear Duration of follow-up: 79 months (mean) 63 months (median)	Patient group: IPF Inclusion criteria: as above Exclusion criteria: NR All patients N: 98 Age (mean): 63 years (range 36-75) M/F: 71/27 Drop outs: 46 died, 10 lost to follow-up	HRCT findings Analysis: Cox proportional hazards regression models used Confounding factors adjusted for: each one of the following CT findings: presence of ground-glass attenuation; airspace consolidation; nodules; interlobular septal thickening; thickening of bronchovascular bundles; intralobular reticular opacities; irregular interlobular septal thickening; nonseptal linear or platelike opacities; presence of honeycombing, cysts, emphysema, architectural distortion, or traction	Traction bronchiectasis-multivariable analysis	HR 1.30 95% CI 1.18-1.43	Funding: NR Limitations: Additional outcomes: Interobserver agreement for CT findings
			Fibrosis score - multivariable analysis	HR 1.10 95% CI 1.03-1.19	

		bronchiectasis; fibrosis score; the extent of disease close to the hilum; and upper, lower, peripheral, dependent, peribronchovascular, and asymmetric predominant distribution.			

Abbreviations: *M/F=male/female, N=total number of patients randomised, SD= standard deviation, HR=hazard ratio, OR= Odds Ratio, RR= Risk Ratio, IPF= Idiopathic Pulmonary Fibrosis, UIP=Usual interstitial pneumonia, ILD=interstitial lung disease, HRCT= high resolution computed tomography, DLCO=Carbon monoxide diffusing capacity, FVC= Forced vital capacity, TLCO=transfer factor for carbon monoxide, 6MWT= 6 minute walking test, PaO2=partial pressure of oxygen in arterial blood, BDI= baseline dyspnoea index, SGRQ= St George's Respiratory Questionnaire, ATS = American Thoracic Society.*

F.3 Pulmonary rehabilitation

Table 61: Almoamary 2012[11]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Almoamary 2012[11] Country of study: Saudi Arabia Study design: retrospective study Who was blinded:	Patient group: The medical records of people referred for pulmonary rehabilitation between 1 July 2004 and 15 January 2008 were reviewed. Only ILD patient data recorded in this table. Inclusion criteria: • ≥18 years, • Diagnoses of bronchiectasis, severe uncontrolled asthma, interstitial lung diseases (ILD)* or scoliosis.	All people People were initially interviewed by a pulmonary rehabilitation physiotherapist as part of the initial assessment on entry in the programme. Adherence to the pulmonary rehabilitation programme required the patient to complete the	6-min. walking distance (m) Mean (SD)	Pre-rehab: 179 (74) Post-rehab: 293 (97) Difference: 114 (58) p value: 0.006	Funding: NR Limitations: Retrospective design Bias Doesn't account for confounding No blinding Additional outcomes: Adherence to rehabilitation programme: 11/21
			Distance on treadmill (m) Mean (SD)	Pre-rehab: 114 (66) Post-rehab: 371 (199) Difference: 257 (163) p value: 0.001	
			Distance on bicycle (m) Mean (SD)	Pre-rehab: 1031 (358) Post-rehab: 2532 (1120) Difference: 1503 (962) p value: 0.004	
			Distance on ergometer	Pre-rehab: 555 (136)	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Setting: pulmonary rehabilitation centre at King Abdulaziz Medical City, Riyadh Duration of follow-up:	• Patient records which were available for 12 months before the start of pulmonary rehabilitation and 12 months after the completion of pulmonary rehabilitation or the last visit (for nonadherent people) Exclusion criteria: • Incomplete medical records • Non adherence to the pulmonary rehabilitation programme • Lack of initial evaluation by the pulmonary rehabilitation therapist All people N: 21 ILD(51 total) Age (mean±SD): 61±9.4 Drop outs: M/F: 6/15 FEV1 (% of predicted): 60.3±16.9 FVC (% of predicted): 64.4 ±15.5 FEV1/FVC: 77.7 ±14.7 PaO2 (mm Hg): 64.8 ±10.7 PaCO2 (mm Hg): 44.5 ±8.2 6-minute walking distance (m):	pulmonary rehabilitation protocol in the outpatient department by attending a 1-hour session, 2–3 times per week, throughout a period of 8–12 weeks for a total of 18–24 sessions. People were discharged from the pulmonary rehabilitation programme at 8 weeks provided that they had attended 18 sessions or until they completed 18 sessions within 8–12 weeks. The pulmonary rehabilitation programme comprised education, exercise and psychosocial support. The exercise programme included a combination of a stationary cycle, treadmill, arm ergometer and stair stepping. The exercise programme was tailored for each	(m) Mean (SD)	Post-rehab: 1238 (522) Difference: 683 (438) p value < 0.001	Right ventricle abnormality: 4/21 Mean (SD) duration of programme for adherent people) (days): 65.6 (12.2) Mean (SD) no. of sessions for adherent people: 12.3 (6.0) Short-acting bronchodilator inhalers (no.), Cumulative prednisone dose (mg), Antibiotic courses (no.) Pre-rehab, Post-rehab, Difference and p values for each. Notes: *The diagnosis of ILD or was confirmed by computed tomography of the chest. The association between different categorical variables
			Emergency department visits (no.) Mean (SD)	Pre-rehab: 1.3 (1.9) Post-rehab: 0.6 (0.9) Difference: –0.7 (0.8) p value 0.280	
			Outpatient department visits (days)	Pre-rehab: 4.7 (2.7) Post-rehab: 2.7 (0.6) Difference: –1.9 (1.6) p value: 0.033	

Study details	Population	Methods	Outcome measures	Effect size	Comments
	189 ±95	patient based on their physiological parameters and the physiotherapist's judgement. Specific exercises for the upper and lower extremities were included, as well as strength and flexibility exercises. Small group education sessions were conducted by the appropriate specialist			was assessed using the chi-squared test, whereas the paired and unpaired t-test was used to test differences between continuous variables. A P-value of < 0.05 was regarded as statistically significant

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 62: Ferreira 2009[141]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Ferreira 2009[141] Country of study: USA	Patient group: Records of people with a diagnosis of ILD who had been referred for PR between January 2003 and March 2008 were retrospectively collected and analyzed from 3 study	All people PR programs were multidisciplinary, outpatient programs that consisted of two or three sessions per week	Borg score (n = 99) mean (SD)	Baseline: 3.6 (2.0) After PR: 2.7 (1.7) Change: -1.0 (1.7) P: > 0.0001	Funding: NR Limitations: No control group Blinding is not reported Data available did not
			UCSD questionnaire (n =29) mean (SD)	Baseline: 57.4 (25) After PR: 49.1 (25) Change: - 8.3 (14)	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Study design: Retrospective observational study Who was blinded: NR Setting: hospital Duration of follow-up: NR	centres Inclusion criteria: a referring diagnosis of ILD and documentation of pre- and post-PR variables Exclusion criteria: NR All people N: 99 Age (mean ±SD): 66± 13 M/F: 54/45 FVC (L, ±SD): 2.2 ±0.9 FVC (% predicted, ±SD): 62 ±20 DLCO (%, ±SD):40 ±14 6MWD (m): NR BDI score:NR SGRQ score (total):NR Lowest oxygen saturation on baseline 6MWT (%,±SD): 89 ±6 Never-smoker: n=41 (41%) LTOT (±SD): 65 ±66 Drop outs: 0	(2 to 3 h each) of exercise and educational activities for 6 to 8 weeks. The exercise sessions included endurance, strength, and respiratory muscles training, along with pacing and breathing techniques. The educational topics included medication and oxygen use, nutrition, panic control and relaxation techniques, as well as psychosocial support and end-of-life issues.		P: 0.005	include information on comorbidities, the onset of a respiratory exacerbation or an acute illness during the PR program, current medications, and specific ILD diagnosis, all of which could potentially influence the results. Data on the level of oxygen used during walk testing were not available for all people. While standard practice was to use a stable level of oxygen throughout the period of PR, it is possible that some people could have received varying levels. Important differences between participating centres could be present that were missed due to inadequate numbers.
			6MWT distance, m (n = 99) mean (SD)	Baseline: 335 (131) After PR: 391 (118) Change: 56 (69) P: > 0.0001	
			CES-D score (n =27) mean (SD)	Baseline: 15.7 (8) After PR: 13.6 (8) Change: 2.2 (5) P: 0.046	
			6MWT distance, % change (n =99) Median (25th percentile, 75th percentile).	Change: 14 (2, 33) P: 0.002	

Study details	Population	Methods	Outcome measures	Effect size	Comments
					Notes: Variables recorded included age, gender, baseline pulmonary function test values, specifically FVC and diffusion capacity of the lung for carbon monoxide (Dlco), smoking history, use of long-term oxygen therapy (LTOT), pre- and post-PR Borg dyspnoea score, pre- and post-PR 6-min walk test (6MWT) distance, and the PR centre attended. Pre- and post-PR University of California San Diego (UCSD) shortness of breath questionnaire scores and Centre for Epidemiologic Studies-Depression (CES-D) scores were available for some people.

Study details	Population	Methods	Outcome measures	Effect size	Comments
					The Borg dyspnoea score, UCSD shortness of breath questionnaire, and the CES-D score were all performed according to published standards.18–20 The 6MWTs were performed according to modified guidelines of the American Thoracic Society.21 Supplemental oxygen was used during the test in people who were already on LTOT or in those who desaturated below 88% All people had ILD diagnosed, which was recorded as idiopathic pulmonary fibrosis (n = 50), unspecified ILD (n =42), scleroderma (n =3), nonspecific interstitial

Study details	Population	Methods	Outcome measures	Effect size	Comments
					pneumonia (n= 2), sarcoidosis (n =1), and lymphangioleiomyomatosis (n= 1).

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 63: Gaunaurd 2011[160]

Study Details	People	Methods	Outcome measures	Effect size	Comments
Gaunaurd 2011[160] Country of study: USA Study abstract of RCT Who was blinded: NR Setting: NR Duration of follow-up: 3 months	Patient group: Veterans with IPF Inclusion criteria: typical IPF Exclusion criteria: NR All people N:6 Drop outs: 0 Age (mean±SD): 67.67±5.68 Male: 5 BMI:29.90±7.08kg/m2	Group 1 – PR* 12 week PR program consisting of educational lectures and supervised exercise: Exercise – 20 minutes of walking and 20 minutes of recumbent cycling. Flexibility exercises consisted of 6 stretches for upper body and lower body and strength training targeted the major muscle groups of the upper and lower body. Sessions were twice a week for 90 minutes Group 2 – control	Change in 6MWD (m) (mean±SD)**	Group 1: 40.33± 53.16 Group 2: -40.33± 57.36 P:NR	Funding: NR Limitations: Abstract – limited information given Additional outcomes: VO2 max by cycle ergometry Notes: *Subjects were required to complete 24 sessions **NCGC calculated

Study Details	People	Methods	Outcome measures	Effect size	Comments

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 64: Holland 2008[185](including unpublished data provided by authors) & Holland 2008 [186]

Study details	People	Methods	Outcome measures	Effect size	Comments
Holland 2008 [185](including unpublished data provided by authors) , Holland 2008 [186] (Cochrane review) & Country of study: Australia Study design: Randomised controlled trial	Patient group: Total n=57, including IPF n=34, IIP n=4 diffuse parenchymal lung disease of unknown cause n=14, granulotamous lung disease n=4. Only IPF people will be reported on in this table. Inclusion criteria: >18 years and sypmtomatic People ambulent and reported dyspnoea on exertion, on stable medical therapy. Exclusion criteria: History of syncope on exertion or any comorbities which precluded exercise	Group 1 - Exercise group 8 week outpatient exercise program, twice weekly supervised sessions by a physiotherapist. Consisting of 30 minutes endurance exercise (cycling and walking) with initial intensity at 80% of walking speed on initial 6-minute walk test and progressed according to protocol. Upper limb endurance and functional strength training for lower limbs also performed. Supplemental oxygen provided for SpO2≥85%. Once established on supervised programme a unsupervised home exercise program prescribed 3 times per week. Aim to achieve 5 exercise sessions per week. Group 2 - Control group	Change in 6-minute walk test immediately following PR (taken from Cochrane)	Group 1: 25.05 Group 2: 8.93 Mean difference: 16.12 95% CI: -13.32, 45.56 P-value: NR	Funding: Victorian Tuberculosis and Lung Association (Holland 2008[185]) Limitations: Large numbers of drop outs The effect of disease aetiology and severity on response to exercise training could not be fully characterised – the study was not powered to adequately assess this outcome. Small sample size Notes: IPF diagnosis criteria in line with international consensus statement Stratified for IPF – raw data
			Chang e in 6-minute walk test long term follow up (taken from Cochrane)	Group 1: -19.15 Group 2: 3.93 Mean difference: -23.08 95% CI: -70.59, 24.43 P-value: 0.34	
			Change in dyspnoea score immediately following training (taken from Cochrane)	Group 1: -0.55 Group 2: 0.23 Standard Mean difference: -0.56 95% CI: -1.26, 0.14 P-value: NR	

Study details	People	Methods	Outcome measures	Effect size	Comments
Who was blinded: Single blinded Setting: outpatient Duration of follow-up 9 &26 weeks	training (such as severe orthopaedic or neurological deficits or unstable cardiac disease). Had participated in a pulmonary rehabilitation programme in the last 12 months All people N: =34 (IPF) Age (mean±SD): NR for IPF alone – all people: 67±13 Drop outs for all participants NR for IPF alone: 8 Group 1 Exercise group N: =30 Age (mean±SD): 70(8) Drop outs for all participants NR for IPF alone: Exercise training programme dropouts: 6 (1=IPF exacerbation, 2=unwell non respiratory, anxiety disorder and back pain 3= didn't want to complete) Loss to follow up :9 week follow up: 2 (declined) 26 week follow up:5	Weekly telephone calls for general health advice and support.	Change in dyspnoea score long term follow up (taken from Cochrane)	Group 1: -0.2 Group 2: -0.21 Mean difference: 0.01 95% CI: -0.79, 0.81 P-value: 0.98	not reported in paper for all outcomes in IPF only group Measured pre and post intervention period. 6 minute walk test and questionnaires repeated at 6 month follow up. Computer generated random number sequence generation. Allocation concealment in a central location, sealed opaque envelope, by an individual unrelated to the study. (randomisation was done separately for IPF to other ILD people to ensure even distribution across groups) Data collector blinded to treatment allocation. Intention to treat analysis, last observation carried forward. All data available at all time points
			Change in quality of life immediately following training (taken from Cochrane)	Group 1: 5.53 Group 2: -8.53 Standard Mean difference: 0.77 95% CI: 0.06, 1.48 P-value: NR	
			Change in quality of life long term follow up (taken from Cochrane)	Group 1: -3.06 Group 2: -10.11 Mean difference: 7.05 95% CI: -8.29, 22.39 P-value: 0.37	
			Six month survival (taken from Cochrane)	Group 1: 2/20 Group 2: 2/14 RR: 0.7 95% CI: 0.11, 4.39 P-value: 0.70	
			SF36 domain: physical functioning (unpublished	Group 1 post treatment : 36.67±21.17 Group1 long term follow up:	

Study details	People	Methods	Outcome measures	Effect size	Comments
	(declined 3 deceased 2) TLCO: 50(19) SF36 domains (mean±SD): Vitality: 40.38±17.43 physical functioning: 40.02±22.45 bodily pain: 59.78±23.21 general health perceptions: 42.19±18.05 physical role functioning: 19.44±28.87 emotional role functioning: 55.56±42.37 social role functioning: 64.35±29.36 mental health: 69.08±16.49 Group 2 Control group N: =27 Age (mean±SD): 67(13) Drop outs for all participants NR for IPF alone: Loss to follow up : 9 week follow up: 2 (1=deceased, 1=Unwell lymphoma) 26 week follow up: 9 (1= declined, 2 =deceased, 2=unwell IPF related 1=unwell lymphoma)		data) mean±SD	31.11±18.93 Group 2 post treatment : 45.56±23.63 Group 2 long term follow up: 38.70±25.89	All data reported in the original paper (Holland 2008[185])did not give IPF data separately from the total
			SF36 domain: physical role functioning (unpublished data) mean±SD	Group 1 post treatment : 25.00±36.69 Group1 long term follow up: 20.37±30.25 Group 2 post treatment : 24.07±39.52 Group 2 long term follow up: 14.81±33.44	
			SF36 domain: vitality (unpublished data) mean±SD	Group 1 post treatment : 42.04±21.76 Group1 long term follow up: 41.48±19.41 Group 2 post treatment : 52.31±17.79 Group 2 long term follow up: 45.38±23.11	
			SF36 domain: bodily pain (unpublished data) mean±SD	Group 1 post treatment : 54.22±30.78 Group1 long term follow up: 55.22±33.93 Group 2 post treatment : 61.51±27.50 Group 2 long term follow up: 63.22±29.23	
			SF36 domain:	Group 1 post treatment :	

Study details	People	Methods	Outcome measures	Effect size	Comments
	TLCO: 49(18) SF36 domains (mean±SD): Vitality: 45.74±19.05 physical functioning: 39.26±23.34 bodily pain: 57.77±27.75 general health perceptions: 45.52±20.42 physical role functioning: 27.78±34.20 emotional role functioning: 55.56±47.14 social role functioning: 65.74±28.08 mental health: 65.48±20.76		general health perceptions (unpublished data) mean±SD	40.23±20.87 Group1 long term follow up: 38.19±22.39 Group 2 post treatment : 42.48±15.97 Group 2 long term follow up: 43.00±23.33	
			SF36 domain: social role functioning (unpublished data) mean±SD	Group 1 post treatment : 67.59±25.77 Group1 long term follow up: 59.26±29.33 Group 2 post treatment : 70.83±29.01 Group 2 long term follow up: 58.33±28.59	
			SF36 domain: emotional role functioning (unpublished data) mean±SD	Group 1 post treatment : 61.73±41.04 Group1 long term follow up: 61.73±42.07 Group 2 post treatment : 61.73±45.95 Group 2 long term follow up: 50.62±47.37	
			SF36 domain: mental health (unpublished data) mean±SD	Group 1 post treatment : 62.96±21.81 Group1 long term follow up: 61.63±19.98 Group 2 post treatment : 76.92±16.30 Group 2 long term follow up:	

Study details	People	Methods	Outcome measures	Effect size	Comments
				72.92±17.65	

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 65: Holland 2012[187]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Holland 2012[187] Design: Observational Study Setting: People recruited from two tertiary centres in Australia Who was blinded?: No one Duration of follow-up: People	Patient group: 44 participants (25 of whom had IPF) Only IPF data presented here Inclusion criteria: Ambulant people reporting dyspnoea on stable medical therapy. Exclusion criteria: History of syncope on exertion; any comorbidities precluding exercise training; participation in a pulmonary rehabilitation program in the last two years IPF people N: 25 Age (mean): 72.9 FVC (% predicted) mean +/- SD: 76.4 +/- 20.3	All people The pulmonary rehabilitation consisted of a twice weekly, eight week exercise program of endurance and strength training which was prescribed and progressed according to a previously defined standard protocol. Supplemental O2 was provided to maintain SaO2 ≥ 85% An unsupervised home exercise program was also prescribed with the aim of achieving five sessions per week in total. People who had been prescribed supplemental O2 were encouraged to use this during home exercise. Participants also attended an education and self-management	Dyspnoea: Change in CRQ dyspnoea domain (at 8 weeks)	Mean (SD): 2.7 (5.6) Significantly improved from baseline p<0.5	Funding: No conflicts of interest declared Limitations: Confounding factors weren't accounted for Small sample size No control Non randomised Additional outcomes: Change in FVC at 6 months Change in DLCO at 6 months No hazard ratios, odds rations or risk ratios reported to inform prognosis. Notes: Only IPF data presented MID: 6MWD 34m (within
			Dyspnoea: Change in CRQ dyspnoea domain (at 6 months)	NS change from baseline	
			Mean improvement in 6MWD (at 8 weeks)	Mean (SD): 21 (58) Significantly improved from baseline p<0.5	
			Change in 6MWD (at 6 months)	NS change from baseline	
			Number of people achieving gains exceeding the MID for 6MWD at 8 weeks	"improvements that exceeded the MID occurred in 40% of participants"	
			Number of people achieving gains exceeding the MID for 6MWD at 6 months	"improvements that exceeded the MID occurred in 35% of participants"	
			Number of people	"improvements that	

undertook 8 weeks of pulmonary rehab and were assessed after 8 weeks and six months	TLCO (% predicted): mean +/- SD: 48.5 (19.1) Drop outs: "6 participants (in whole group) did not complete the rehab program due to respiratory illness (n=1), other illness (n=1), musculoskeletal pain (n=1) and lack of motivation (n=3). Two of these participants (both with IPF) declined further participation in the study" One participant with IPF died prior to 6 month follow up	program.	achieving gains exceeding the MID for CRQ dyspnoea at 8 weeks	exceeded the MID occurred in 59% of participants"	our MID range 24-45m) MID: CRQ dyspnoea 2.5 points (we use standard MIDs)
			Number of people achieving gains exceeding the MID for CRQ dyspnoea at 6 months	"improvements that exceeded the MID occurred in 24% of participants"	

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 66: Jastrzebski 2006[213]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Jastrzebski 2006[213] Country of study: Poland Study design: cohort	Patient group: ILD Inclusion criteria: · interstitial lung disease was diagnosed on the basis of radioclinical criteria · people reported at least 2 years of disease symptoms · people did not require home oxygen therapy	All people The rehabilitation programme was composed of 4 weeks of rehabilitation held in the hospital and later continued by people themselves at home. The exercise programme was formed on the basis of the American Society, the British Thorax Society, and the American	Dyspnoea (MRC scale)-5 grade scale	Baseline: 2.3±0.8 After rehab: 2.0±0.9 P: 0.06	Funding: NR Limitations: No baseline data provided Confounding factors weren't accounted for Small sample size No control Non randomised
			Dyspnoea (oxygen cost diagram)	Baseline: 72.2±14.6 After rehab: 77.2±15.9	
			Dyspnoea (baseline dyspnoea index): sum of functional impairment, magnitude and effort and	Baseline: 6.3±2.8 After rehab: 6.8±3.3	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Who was blinded: no one Setting: Department of Lung diseases and Tuberculosis of an academic hospital in Zabrze, Poland Duration of follow-up: 6 weeks	· people were able to perform exercises on a bicycle ergometer · treatment with no more than 20 mg of prednisone per day · people were at a stable stage of disease, free of infection Exclusion criteria: All people N: 38 (began programme; 31 completed)* M/F: 19/12 Mean age: 48.7 years Drop outs: 7	Society of Cardiologic and Respiratory Rehabilitation recommendations, which were for COPD people. The people were informed about the rules and aims of the planned programme. A diary was provided in which they were obliged to note any deviations from, or problems with, the execution of the exercise programme. In the hospital environment, the programme was introduced to the patient under the supervision of an experienced instructor of rehabilitation, and exercise was preceded by instruction and demonstration of the planned tasks. The timing and intensity of the exercise program was prepared individually for each patient. The programme consisted of general exercise, performed twice a week for 30 min, (movements of the thorax, correctional exercise, isometric exercise), respiratory muscle exercise, consisting of 6 series of 5-breath cycles interspersed with	magnitude of task		Additional outcomes: BDI domains – functional impairment, magnitude of task, magnitude of effort Notes: 3 people terminated the rehabilitation due to disease exacerbation caused by infection that led to hospitalization, 2 people resigned from the training programme after 2 and 4 weeks because of discouragement to exercise, although they did not manifest any side effects, and 2 others were excluded from the analysis, since they did not report to the control examination due to personal reasons. *THE SAMPLE INCLUDED: · 21 people with idiopathic interstitial pneumonia · 13 people with idiopathic pulmonary fibrosis · 8 people with nonspecific
			Dyspnoea (Borg scale of 1 to 10)	Baseline: 3.0±1.4 After rehab: 2.5±1.4	
			SF36 domain: physical functioning (mean-taken from graph)	Baseline: 55 After rehab:65 P: <0.05	
			SF36 domain: physical role functioning (mean-taken from graph)	Baseline: 40 After rehab:55 P: NR	
			SF36 domain: vitality (mean-taken from graph)	Baseline: 53 After rehab:58 P: <0.05	
			SF36 domain: bodily pain (mean-taken from graph)	Baseline: 69 After rehab:67 P: NR	
			SF36 domain: general health perceptions (mean-taken from graph)	Baseline: 38 After rehab: 41 P: NR	
			SF36 domain: social role functioning (mean-taken from graph)	Baseline: 58 After rehab:70 P: <0.05	

Study details	Population	Methods	Outcome measures	Effect size	Comments
		1-min rest periods (altogether 30 breaths), run on Threshold IMP produced by Healthdyne Technologies (UK), and bicycle ergometer training, performed once a day for 15 min with a pretested 60% max load in Watts.			interstitial pneumonia · 4 people with pulmonary fibrosis due to allergic alveolitis (chronic form) · 5 people with pulmonary fibrosis due to mix collagenosis · 1 patient with pulmonary fibrosis due to silicosis
			SF36 domain: emotional role functioning (mean-taken from graph)	Baseline: 69 After rehab:80 P: NR	
			SF36 domain: mental health (mean-taken from graph)	Baseline: 62 After rehab:68 P: <0.05	
			SGRQ domains: symptoms (mean-taken from graph)	Baseline: 45 After rehab:46 P: NR	Overall scores not provided for SF-36 QoL (SF-36)- graph only SGRQ- graph only
			SGRQ domains: activity (mean-taken from graph)	Baseline: 52 After rehab:45 P: <0.03	
			SGRQ domains: influence (mean-taken from graph)	Baseline: 47 After rehab:37 P: <0.03	
			SGRQ total domains (mean-taken from graph)	Baseline: 47 After rehab:42 P: <0.03	

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 67: Kozu 2011[253]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Kozu 2011[253] Country of study: Japan Study design: prospective nonrandomized open trial Who was blinded: no-one Setting: Department of Rehabilitation Medicine, Nagasaki, Japan Duration of follow-up: 6 months	Patient group: IPF and COPD. Only results of IPF group reported in this table Inclusion criteria: Subjects were eligible to participate if they reported dyspnoea on exertion leading to a limitation in daily activities (Medical Research Council [MRC] grade > 1) and were on stable medical treatment. The diagnosis of IPF was based on published criteria- ATS guidelines 2000. Exclusion criteria: Individuals with collagen vascular disease, occupational lung disease, sarcoidosis, hypersensitivity pneumonitis and other idiopathic interstitial pneumonias were excluded. Other exclusions were MRC grade 5, severe orthopaedic or neurological disorders limiting exercise performance, unstable cardiac disease, inability to understand or complete questionnaires and previous	All people Prior to recruitment, subjects in both groups were required to be clinically stable for at least 4 weeks. All people were under the care of a respiratory physician. Medical treatment, including dose of oral corticosteroids and immunosuppressives was not changed during the rehabilitation Subjects attended an 8-week outpatient programme comprising two classes each week, (90 minutes duration), that included exercise training, breathing retraining, and education. During each class, subjects performed 40 - 50 minutes of exercise supervised by a physiotherapist. Subjects also were instructed to undertake daily exercise at home and were encouraged to continue their home-based program at the end of the 8 weeks. Adherence with the home programme was assessed using a diary card.	Dyspnoea (MRC grade)	Baseline (n=36): 3.0 ±0.8 8 weeks (n=36): 2.5±1.1 P=<0.01 6 months (n=30) : 2.9±1 P= NR	Funding: NR Limitations: Large number of drop outs 20% drop out rate in IPF group (not including follow up period) Non randomised Blinding not reported Inconsistencies in reporting some data (when comparing IPF performance with COPD) Control group composed of COPD people not IPF people receiving usual care Small sample Does not account for all confounding factors e.g. pulmonary hypertension. Additional outcomes: Adverse events TDI focal score Muscle force Activities of daily living score Notes:
			Exercise capacity (6MWD)	Baseline (n=36): 323±109 8 weeks (n=36): 340±122 P=<0.01 6 months (n=30) : 320±106 P= NR	
			SF36 domain: physical functioning (mean±SD)	Baseline (n=36): 38.6±19 8 weeks (n=36): 40.6±22.6 P=NR 6 months (n=30) : 37.8±23 P= NR	
			SF36 domain: physical role functioning (mean±SD)	Baseline (n=36): 34.9±21.5 8 weeks (n=36): 35.9±20.7 P=NR 6 months (n=30) : 30.4±23.7 P= NR	
			SF36 domain: vitality (mean±SD)	Baseline (n=36): 43.1±20 8 weeks (n=36): 43.9±21 P=NR 6 months (n=30) : 42.1±23.6 P= NR	
			SF36 domain: bodily pain	Baseline (n=36): 66.1±30	

Study details	Population	Methods	Outcome measures	Effect size	Comments
	participation in a pulmonary rehabilitation programme. All people N: 90 Drop outs: Group 1 (IPF)- only results of this group reported in this table N: 45 (36 completed programme(discontinued due to exacerbation =3, didn't wish to complete = 3 other reasons =3), 30 completed 6 month follow-up (deceased = 4 declined = 2)) Age (mean): 67.5 ±7.8 Gender, M/F: 37/8 Time since diagnosis, years: 1.8±1.8 Oral corticosteroids 20 (44%) Cough: 30 (67%) FVC, litres: 2.0 ±0.6 FVc, % predicted: 68.6 ±16 DLCO:, ml/min/mmHg: 6.0±2.5 DLCO, % predicted: 38.8±20 Drop outs: 9 (exacerbation: 3, did not wish to complete: 3, other reasons:3)	Exercise training included stretches and endurance and strength training. Lower limb endurance training was performed using a cycle ergometer with the initial workload prescribed at 50% of the PWR achieved on the baseline cycle ergometer test. In the early stages of the program, cycling was limited to 5 to 10 minutes and progressively increased, within symptom tolerance, to 20 minutes of continuous cycling. Once subjects had achieved 20 minutes cycling, the workload was increased. Upper limb endurance training comprised repetitive bilateral shoulder flexion and abduction using a light weight and synchronized with expiration for 2 minutes. Strength training was accomplished using free weights or the subject's own body weight. One set of 10 repetitions was initially prescribed increasing to 3 sets when the subject could perform the exercises without any difficulty. Arterial oxygen saturation was monitored during each session, and supplemental oxygen was given as necessary, to maintain arterial oxygen saturation above 85%. We recorded the duration of cycle-	(mean±SD)	8 weeks (n=36): 63.4±28.1 P=NR 6 months (n=30) : 62.5±30.3 P= <0.05	No adverse events were recorded during this programme. Supervised sessions attended by IPF people: 13.3±3.8 p=0.24 Average number of home based exercise sessions completed each week 3.9±1.9 p=0.59 20% drop out rate in IPF group
			SF36 domain: general health perceptions (mean±SD)	Baseline (n=36): 37.1±20 8 weeks (n=36): 36.9±21.1 P=NR 6 months (n=30) : 34.4±21.5 P= <0.05	
			SF36 domain: social role functioning (mean±SD)	Baseline (n=36): 51±23.8 8 weeks (n=36): 50.3±25.3 P=NR 6 months (n=30) : 45.8±26.9 P= <0.05	
			SF36 domain: emotional role functioning (mean±SD)	Baseline (n=36): 39.6±30.7 8 weeks (n=36): 38.7±31.3 P=NR 6 months (n=30) : 35.8±29.8 P= NR	
			SF36 domain: mental health (mean±SD)	Baseline (n=36): 50.7±18.7 8 weeks (n=36): 52.6±20.5 P=NR 6 months (n=30) : 47.5±21.8 P= NR	

Study details	Population	Methods	Outcome measures	Effect size	Comments
	Group 2 (COPD- control)- results not reported in this table N: 45 (40 completed programme, 37 completed 6 month follow-up) Age (mean): Drop outs: 5 (exacerbation: 1, did not wish to complete: 2, other reasons: 2)	based exercise (in minutes) and workload (in Watts) of all subjects for each of the exercise sessions. Breathing retraining consisted of relaxation with breathing control, pursed-lip breathing and pacing during exercise training and ADL. The rationale for pursed-lip breathing in the IPF cohort was to assist subjects to control their breathing by reducing respiratory frequency. All subjects received the same instructions. The education component was provided by a physiotherapist at each class and consisted of the benefits and importance of daily exercise, pacing and energy conservation techniques to manage ADL and self-management strategies for coping with an exacerbation. Subjects were considered to have completed the programme if they attended at least 12 (75%) of the 16 supervised sessions. At the end of the 8 week programme, all subjects were encouraged to			

Study details	Population	Methods	Outcome measures	Effect size	Comments
		continue with their home exercise program however no formal maintenance programme was provided.			

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Table 68: Naji 2006[338]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Naji 2006[338] Country of study: Ireland Study design: Retrospective chart review Who was blinded: NR Setting: Hospital	Patient group: People with restrictive lung disease referred to a pulmonary rehabilitation centre over the past 8 years. Only the data for ILD people is presented here. Inclusion criteria: NR Exclusion criteria: Significant airflow obstruction Noncompliant Unable to perform pulmonary function tests or exercise endurance tests	All people People initially admitted to hospital for 3 days for baseline assessments and to commence on the programme. The programme consisted of exercise and education * was continued post discharge 2/week over a period of 8 weeks.	Shuttle test (m) mean±SD	Baseline**:171±102 8 weeks:232±118 1 year: NR	Funding: NR Limitations: Some figures related to dropouts and survival data doesn't add up correctly. Very unclearly reported. Small sample size Single centre High dropout rate – 46% Blinding is not reported Retrospective observational study- No control group Additional outcomes: Survival (accurate and reliable data was not extractable from the paper) treadmill test Anxiety and depression were also measured using the hospital anxiety questionnaire. Results for all outcomes for all people with
			CRDQ (dyspnoea) Median (ranges)	Baseline**: 15.6 (9.7, 22.6) 8 weeks:17.2(14.6, 27.1) 1 year: NR	
			SGRQ Median (ranges)	Baseline**: 48.1 (23, 82) 8 weeks: 26.4(17.4, 69.4) 1 year: NR	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Duration of follow-up: 8 weeks and 1 year	All people N: 35 ILD (19 people reported on at 8 weeks and 10 at 1 year) Drop outs: 15 (excluded from analysis) Age (mean±): 66.5±11.3 M/F: nr FVC (% predicted): 66.7±20.7 DLCO (%): 42.5±14 Borge scale: 3.4(1.8,5.5) SGRQ score (total):48(27.6, 67.9) CRDQ: 16(12.6,22.6) BMI kg/m²: 26.7±4.9 shuttle test (m):206±108				restrictive lung disease this included the ILD people Notes: Of the 35 ILD people 28 had IPF * described elsewhere- Connor MC et al efficacy of pulmonary rehabilitation in an Irish population. Ir Med J.2001; 94(2):46-48. PFT testing conducted according to ERS guidelines the treadmill and shuttle test were performed. QOL was assessed using the chronic respiratory disease questionnaire and SGRQ. Only data from people who were compliant is described – compliance: measured as attendance at 24 exercise sessions and at required reassessments at 8 weeks and 1 year. Available case analysis **The baseline data given in the effect size column is reported for the same people who reached 8 weeks not all subjects who enrolled

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 69: Nishiyama 2008[355]& Holland 2008[186]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Nishiyama 2008[355] & Holland 2008[186](Cochrane review) Country of study: Japan Study design: RCT Who was blinded: NR Setting: Outpatient clinic Duration of follow-up NR	Patient group: consecutive people referred to an outpatient clinic between 2000 and 2004 Idiopathic pulmonary fibrosis n=28 Inclusion criteria: <75 years Diagnosis of IPF* Shortness of breath on effort Stable clinical condition with no infection or exacerbation in the previous 3 months Exclusion criteria: Severe co morbid illness Collagen vascular diseases Need for long term oxygen therapy Previous treatment with corticosteroids/ immunosupressents Group 1:Exercise group n=13**,	All people: no patient received any treatment with steroids or immunosupressives during the study period. Group 1 :Exercise group 9 week outpatient exercise program, twice weekly supervised sessions. Exercise on treadmill at 80% of walking speed on initial 6-minute walk test, or on cycle ergometer at 80% of initial maximum workload. Strength training for limbs using elastic bands for approximately 20 minutes. Supplemental oxygen administered to achieve SpO2>90%. Some educational lectures included (content unspecified). Group 2: Control group Not specified	6-minute walk test (taken from Cochrane review)	Group 1: 42 SD:50.8 Group 2: -4 SD:57.7 Mean difference: 46 95% CI: 5.81, 86.19 P-value: NR	Funding: Supported by the Japanese Ministry of Health, Labour and Welfare Limitations : Blinding of investigators not reported Sequence generation unclear Selective reporting may be a problem, due to insufficient data it is not possible to determine if all data was made available. Additional outcomes: FVC, FEV1, TLC, PaO2, PaCO2 Notes: All measured at baseline and 10 weeks. Allocation concealed using sealed envelopes that had been prepared
			dyspnoea score (taken from Cochrane review)	Group 1: 0 SD:1.3 Group 2: 0.4 SD:1.5 Mean difference: -0.28 95% CI: -1.02, 0.47 P-value: NR	
			St George's Respiratory Questionnaire (SGRQ) (total only - taken Cochrane review – exercise group marked as 2.9 and control as -3.1. Reported SMD in cochrane)	Group 1: 2.9 SD:14.13 Group 2: -3.1 SD:18.25 Mean difference: NR 95% CI: NR P-value: NR	
			SGRQ domains: symptoms mean±SD (as reported in original study)	Group 1baseline : 53.4±25.8 Group1 post PR: 56.4±22.3 Group 2baseline: 38.0±25.8 Group2 post PR: 40.6±21.2 95% CI: NR	

Study details	Population	Methods	Outcome measures	Effect size	Comments
	m/f: 12/1 age 68(9) years, DLCO 59.4(16.7)%predicted 6MWD:385±116 Group 2: Control group n=15, m/f:9/6 age 65(9) years, DLCO 48.6(16.7)%predicted 6MWD:476±128			P-value: NR	prior to the study. **Two people randomised to exercise training but withdrew before baseline data collected. *The diagnosis of IPF was made according to ATS/ETS statement.
			SGRQ domains: activity mean±SD (as reported in original study)	Group 1baseline : 62.5±16.9 Group1 post PR: 64.7±17.1 Group 2baseline: 50.4±26.2 Group2 post PR: 54.0±22.6 95% CI: NR P-value: NR	
			SGRQ domains: impact mean±SD (as reported in original study)	Group 1baseline : 36.5±17.5 Group1 post PR: 39.7±17.6 Group 2baseline: 29.9±23.7 Group2 post PR: 32.9±23.5 95% CI: NR P-value: NR	
			SGRQ total domains mean±SD (as reported in original study) reported in original study)	Group 1baseline : 47.3±17.4 Group1 post PR: 50.2±16.3 Group 2baseline: 37.8±22.725.8 Group2 post PR: 40.9±20.7	

Study details	Population	Methods	Outcome measures	Effect size	Comments
				95% CI: NR P-value: NR	

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 70: Ozalevli 2010[373]

Study Details	Population	Methods	Outcome measures	Effect size	Comments
Ozalevli 2010[373] Country of study: Turkey Study design: prospective cohort Who was blinded: no-one Setting:	Patient group: IPF, diagnosed using ATS/ERS criteria Inclusion criteria: Clinically stable Treatment with no more than 20mg of prednisone per day No pulmonary infections in the last 6 weeks No serious cardiological or psychological problems Not receiving supplementary O2 therapy No neurological, inner ear or orthopaedic disease Able to ambulate without assistance or assistive devices	All people Home-based PR programme lasting 12 weeks. All people received a booklet giving instructions on the programme. The programme consisted of pursed-lips breathing, thoracic expansion exercises, upper and lower extremity exercises combined with breathing control and a walking programme (15-30 min/day). Breathing control training, coping strategies to deal with shortness of breath and relaxation training were given. People were instructed to	6MWD	Before: 390.3 After: 430.5 P=0.04	Funding: NR Limitations: Small study size No blinding or randomisation Did not account for confounding factors No control group Generalisability Additional outcomes: FEV1 FEV1/FVC 6MWD-SpO2 and heart rate, dyspnoea, leg fatigue
			Dyspnoea (MRC scale)	Before:2.3±1.2 After: 1.4±1.3 P=0.003	
			SF36 domain: physical functioning (mean±SD)	Before: 57.00±5.7 After: 58.7±7.3 P:0.24	
			SF36 domain: physical role functioning (mean±SD)	Before: 56.00±1.7 After: 68.3±1.6 P:0.01	
			SF36 domain: vitality (mean±SD)	Before: 52.00±4.9 After: 55±4.2 P:0.40	
			SF36 domain: bodily pain	Before: 25.00±2.6	

Home-based, Izmir, Turkey Duration of follow-up: 12 weeks	Willing to participate in the study Exclusion criteria: Obstructive lung disease (FEV1/FVC <80%) Acute coronary artery disease Collagen vascular disease Pneumoconiosis Sarcoidosis Cancer Non-parenchymal restrictive lung disease Other severe co morbid conditions All people N: 17 (15 completed) Drop outs: 2 (infectious disease) Age (mean): 62.8±8.5 M/F: 10/5 Disease duration, years: 5.0 ±3.8 Smoking history: 6/13 (40%)	perform all exercises 5 days a week, in 3 sessions per day with 10 repeats. Supervision was done by phone calls once a week and a daily exercise query.	(mean±SD)	After: 72±2.2 P:0.40	FVC DLCO Notes: Those who did not complete the home based pulmonary rehabilitation programme or voluntarily left were excluded 6MWT administered to ATS criteria SF-36 (no total provided) Mean number of weekly completed session: 13.2±2.1
			SF36 domain: general health perceptions (mean±SD)	Before: 67.30±4.6 After: 74±4.7 P:0.04	
			SF36 domain: social role functioning (mean±SD)	Before: 75.80±2.7 After: 89.1±1.8 P:0.17	
			SF36 domain: emotional role functioning (mean±SD)	Before: 29.00±1.3 After: 65±1.4 P:0.02	
			SF36 domain: mental health (mean±SD)	Before: 49.90±6.7 After: 56.8±5.4 P:0.14	

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 71: Rammaert 2011 [404]

Study	Population	Methods	Outcome measures	Effect size	Comments

Details					
Rammaert 2011[404] Country of study: France Study design: Prospective observational Who was blinded: no-one Setting: Calmette Hospital (part of Lille University Hospital) Duration of follow-up: 8 weeks	Patient group: stable people with IPF Inclusion criteria: ATS/ERS diagnosis of IPF The ability to perform a walk test and use a cycle ergometer The motivation and agreement of the patient for the setting up of a home based rehabilitation programme Exclusion criteria: Contraindications to functional exercise testing Acute exacerbation of IPF Changes in therapy planned in the coming 8 weeks People not requiring oxygen therapy during exercise All people N: 17 began programme, 14 completed, 13 evaluable Age (mean): 67±13 Male: 9/13 (62%): Drop outs: 3 (3 presented exacerbation of fibrosis- 2 of whom died; one patient developed a gluteal abscess)	All people All examinations were carried out as part of the usual management of people with IPF. Pulmonary rehabilitation was based on the French Society of Pneumonology recommendations for people with COPD. All people underwent prior cardiopulmonary exercise testing to establish a personalised prescription for training. Home-based PR was carried out for 8 consecutive weeks, lasting 30-45 minutes per day and included: Endurance training Muscle strengthening Activities of daily living, walking and learning to climb stairs Compliance with the programme was evaluated every week by a team member. A patient education programme was also implemented with a picture folder and fact sheets.	6MWT breathing room air (n=13)	Before: 383±115 After: 375±01	Funding: NR Limitations: Small sample size QoL scores not adequately reported Doesn't account for confounding Large number of drop outs – 41% Generalisability – single centre No comparison group Additional outcomes: Cycle endurance 6 minute step test Timed up and go Nadir SpO2 Chair stands FVC, DLCO and FEV1 before and after VAS domains: impact on everyday life, treatment constraints anxiety, breathlessness, quality of sleep, physical capabilities and sense of wellbeing. Notes: Oxygen therapy was
			Dyspnoea (MRC score)- median	Before: 1.5 (1-3) After: 2 (1-3)	
			Dyspnoea (Borg scale) evaluated during step test	Before:4 (2-8) After: 3 (2-9)	
			Visual Analogue Scale (total)- assessing anxiety and sense of wellbeing.	Before: 38±8 After: 42±12 p=0.004	
			QoL (SF-36, SGRQ & HAD)	"Perceived physical limitation during exercise as described in the SF-36 decreased after PR (P=0.047). no significant differences were observed for the other SF-36 parameters, the SGRQ or the HAD scale	

					prescribed during exercise to improve the physical performance of the people when transcutaneous oxygen saturation measured during the 6MWT was less than 90%. The flow rate was adjusted depending on the exercise level to obtain a spO2 above or equal to 90%

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 72: Swigris 2011[465]

Study Details	Population	Methods	Outcome measures	Effect size	Comments
Swigris 2011[465] Country of study: USA Study design: pilot cohort Who was blinded: no-one	Patient group: IPF, diagnosed by ATS/ ERS criteria (2000) Inclusion criteria: Diagnosis of IPF: no identifiable cause for lung fibrosis, and UIP lung injury confirmed by the characteristic pattern on HRCT or via SLB. PR not completed within the last 2 years Ability to walk Exclusion criteria: conditions that precluded the safe completion of	All people PR programme consisting of 18 sessions over 6-8 weeks, in accordance with American Thoracic Society standards and based on the NETT (National Emphysema Treatment Trial Research Group) PR programme. Consisted of: exercise (aerobic and resistance training, instruction on breathing techniques, pacing and energy conservation). These were individualised based on patient status and estimated ability.	6MWD (feet)	Baseline:906±111 After PR: 1108±164 Difference:202±135 P:0.01	Funding: Dr Swigris was partly supported by National Institutes of Health Career Development Award. The study was partly supported by an award form the Mordecai Palliative Care Research Fund and partly by Colorado Clinical and Translational Science Award. Limitations: Small sample size Substantial % of drop outs
			General anxiety disorder-7 (a 7 item questionnaire, score from 0-21, with a higher score indicating more anxiety. 5-9= mild anxiety, 10-14= moderate anxiety, 15-21= severe anxiety)	Baseline:2.7±0.8 After PR: 1.3±0.5 Difference: -1.4±0.5 P: 0.1	
			Patient Health Questionnaire- 8 (8	Baseline:3.4±0.0 After PR: 2.5±0.7	

Study Details	Population	Methods	Outcome measures	Effect size	Comments
Setting: 6 centres certified by the American Association of Cardiovascular and Pulmonary Rehabilitation Duration of follow-up: 6-8 weeks	PR (e.g. unstable coronary artery disease) All people N: 21 had baseline data collected, 14 had data collected after PR Drop outs: 7 (2 died with IPF exacerbation, 4 did not enrol in PR, 1 withdrew from PR due to back pain) Age (mean): 71.5±7.4 Male: 18 FVC (% predicted): 73±22 (41-113) DLCO (%): 38±13 (12-63) 6MWD (m): 906±488 (110-1755) SLB: 14 Supplemental O2, 24 h/d: 7 Supplemental O2 only on exertion: 7 Ever smoked: 13 Taking prednisone: 7 Stable coronary artery disease: 3 Systemic hypertension: 7 Osteoarthritis: 13 COPD: 7 Diabetes mellitus: 5	The aerobic component was begun at a level to achieve a heart rate 60% of the predicted maximum for the age; intensity and duration was gradually increased to build tolerance and confidence, with the goal of reaching maximum tolerated workload during each exercise period (goal at least 30min of continuous exercise). Prior to PR as part of routine care, each subject performed walk oximetry with oxygen titration to maintain Spo2 of ≥90%. During PR Spo2 and titrated oxygen flow were monitored to ensure saturation was >89% The education component included sessions on oxygen use, medications, relaxation, psychosocial support, energy, nutrition and end of life issues.	item questionnaire from 0-24, where a higher score indicates more severe depression. 5-9=mild, 10-14= moderate, 15-19= moderately severe, 20-24= severe depression)	Difference: -0.9±0.7 P:0.2	PR was paid for through people' insurance therefore were a highly motivated group Additional outcomes: Fatigue severity scale Pittsburgh Sleep total Notes: 7/21 people had co-existing COPD The comparison group was COPD people results taken from another trial (results not reported in this table)
			SF36 domain: physical functioning (mean±SE)	Baseline: 31.9±2.4 After PR: 33.1±2.8 Difference: 1.2±2.2 P:0.6	
			SF36 domain: physical role functioning (mean±SE)	Baseline: 36.4±2.3 After PR: 38±2.8 Difference: 1.5±2.0 P:0.5	
			SF36 domain: vitality (mean±SE)	Baseline: 47.2±2.2 After PR: 50.8±2.6 Difference: 3.6±2.2 P:0.1	
			SF36 domain: bodily pain (mean±SE)	Baseline: 45±2.2 After PR: 47.6±2.7 Difference: 2.7±2.7 P:0.3	
			SF36 domain: general health perceptions (mean±SE)	Baseline: 38.3±1.7 After PR: 39.8±2.9 Difference: 1.4±2.8 P:0.6	

Study Details	Population	Methods	Outcome measures	Effect size	Comments
			SF36 domain: social role functioning (mean±SE)	Baseline: 45.1±2 After PR: 47.1±3 Difference: 1.9±2.2 P:0.4	
			SF36 domain: emotional role functioning (mean±SE)	Baseline: 45.7±2.6 After PR: 43.8±4 Difference: -1.9±4.3 P:0.7	
			SF36 domain: mental health (mean±SE)	Baseline: 51.8±2 After PR: 53.3±1.4 Difference: 1.6±1.7 P:0.4	

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

F.4 Best supportive care

F.4.1 Oxygen management

Table 73: Crockett 2001[92] & Zielinski 2000[509]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Crockett 2001 [92] & Zielinski 2000 [509]	Patient group: Patients diagnosed with interstitial pulmonary Fibrosis. The patients were followed over a four year period.	Compared long-term oxygen therapy to a control, no oxygen therapy group	Mortality at 12 months	Group1: 7/37 Group 2: 8/25 p value: 0.24	Funding: NR Limitations:
			Mortality at 24	Group1: 23/37	

Study details	Population	Methods	Outcome measures	Effect size	Comments
review of Braghiroli 2000 unpublished data Country of study: International Study design: Controlled multi-centre study Who was blinded: NR Setting: NR Duration of follow-up: 3 years	(study commenced in 1988) Inclusion criteria: either gender under 79 years of age diagnosis on X-ray examination of interstitial pulmonary Fibrosis, clinically stable, not previously treated with oxygen, Arterial oxygen tension (PaO2) between 45-60 mm Hg (6.0-8.0 kPa) on 4 consecutive weekly determinations. Total lung capacity (TLC) was < 80% predicted Exclusion criteria: without other major causes of morbidity and mortality such as malignancy, unstable angina, or recent myocardial infarction, congestive cardiac failure, alcoholism, recent pulmonary embolism, diabetes or pregnancy. All patients N: 62 Drop outs:	Group 1 Treatment with long-term domiciliary oxygen therapy Group 2 no oxygen therapy All patients Pharmacological treatment was kept steady for as long as possible during the study Pulmonary artery catheterisation was performed using a swan-ganz thermodilution catheter. After initial measurements were taken, patients received oxygen at a flow of ≥2L/min to increase PaO2 to > 65mmHg. Second measurements were taken after one	months Mortality at 3 years	Group 2: 12/25 p value: 0.27 Group1: 34/37 Group 2: 23/25 p value: 0.99	The method of randomisation for the study was not stated. The method of blinding was not described. However, random sampling was set up by blocks, each with six cases allocated to the treatment group and five cases to the control group Missing baseline data per group Additional outcomes: Pulmonary artery pressure, cardiac output, pulmonary vascular resistance, arterial oxygen tension for patients on oxygen and room air. Mortality at 12 months: Peto Odds Ratio (Peto, Fixed, 95% CI): 0.50 [0.15, 1.61], Mortality at 24 months: Peto Odds Ratio (Peto, Fixed, 95% CI): 1.76 [0.64, 4.86], Mortality at 3 years:Peto Odds Ratio (Peto, Fixed, 95% CI): 0.99 [0.16, 6.26] Notes: Crockett 2001 [92] & Zielinski 2000 [509] present the findings of the unpublished work of Braghiroli et al. information has been taken from both reviews. Results and

Study details	Population	Methods	Outcome measures	Effect size	Comments
	Age: 62±7 Mean vital capacity: 51±13% of predicted Ratio of FEV in the first second to the VC: 103±12% Total lung capacity: 65±18%of predicted DLCO: 43±10% of predicted Mean PaO2: 54±10 mmHg Mean PaCO2: 36±5 mmHg Group 1 N: 37* Age (mean): NR M/F: 17/20 Drop outs: 0 Group 2 N: 25* Age (mean): NR Drop outs: 0 M/F: 14/11	hour of oxygen			information on methodology have been taken from Crockett 2001 [92] and only information on metholodoly was taken from Zielinski 2000 [509] Forty nine of the patients (28 treated and 21 controls) had a diagnosis of idiopathic pulmonary fibrosis, and 13 (9 treated and 4 controls) had pulmonary fibrosis secondary to other diseases Only mortality data with both disease groups combined was provided for the included patients The effect of oxygen therapy on physiological parameters was not indicated & data on quality of life was not reported in crockett 2001 review of Braghiroli 2000 study.

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 74: Obi 2010[363]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Obi 2010[363] Design: Retrospective review Country of study: Setting: Inova Fairfax Hospital, VA, USA Duration of follow-up: Comparison of 6MWT done with and without O2 on the same day	Patient group: Advanced chronic lung diseases Only IPF data presented Inclusion criteria: NR Exclusion criteria: NR IPF Patients N: 24 Baseline characteristics: NR Drop outs: NR	Group 1: With Supplementary O2 Group 2: Without O2	Mean difference change in 6MWD (m) between groups	19.17 NS difference	Funding: NR Limitations: Abstract only No baseline characteristics No blinding No randomisation Small sample size No description of sample given Additional outcomes: Mean O2 requirement Notes: Abstract only
			Mean difference change in lowest SaO2 (%) between groups	4.83 p<0.05	
			Dyspnoea: Mean change in Borg max (score) between groups	-1.04 p<0.05	

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 75: Swinburn 1991[468]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Swinburn 1991 [468] Country of study: UK Study design: Double-blinded crossover study Who was blinded: Patients and investigator Setting: Hospital inpatient ward Duration of follow-up: N/A	Patient group: ILD including cryptogenic fibrosing alveolitis (8 patients) amiodarone lung toxicity (1 patient) hypersensitivity pneumonitis (1 patient) All patients severely disabled by respiratory distress and breathless at rest. Each patient studied whilst a hospital inpatient and claimed subjective benefit from supplemental oxygen on the ward. Inclusion criteria: NR Exclusion criteria: NR All patients N: 10 Drop outs: 0 Age (SE): 56.3 (2.2) M/F: 6/4 SaO2 %: 85.5 (SE 1.7)	The patients were studied in a quiet room while comfortably seated with good lumbar and lateral support. Each subject received 28% oxygen or air through the same face mask using the same source flow rate (4L/min). 100% oxygen and air were supplied from gas cylinders. Arterial oxygen saturation was measured using an ear oximeter Measurements were made during four periods of 10 min with each gas given twice in a randomised sequence. For a run to be acceptable SaO2 had to remain stable (±1%) over the second 5 min of each period. A 5 min washout period during which the mask was removed separated each of the four study periods. All measurements were recorded by an assistant behind a screen. At the end of each gas breathing period immediately after the measurements were taken and before the removal of the mask the patient was asked whether the gas helped	SaO2, % Visual Analogue Scale (100mm VAS)	Group1: 94.7 (SE 0.9) SD: 2.85# Group 2: 85.5 (SE 1.7) SD:5.38# p value: <0.01 Group1: 30.2 (SE 5.1) SD:16.13# Group 2: 48.1 (SE 4.4) SD:13.91# p value: <0.05	Funding: NR Limitations: Baseline VAS scores not provided Small sample Order effects Carry-over between treatments- wash out period long enough? Potential for confounding Method of randomisation not stated Additional outcomes: Effect of oxygen on ventilation, tidal volume, respiratory rate, and effect of oxygen on the same parameters in COAD patients Notes: Oxygen management Order effects were

Study details	Population	Methods	Outcome measures	Effect size	Comments
		his/her breathing (y/n) and to record the severity of breathlessness on a 100-mm visual analogue scale with limits marked "not at all breathless" and "extremely breathless" Group 1 (oxygen) 28% oxygen by venture face mask Group 2 (air) air by venturi face mask All patients Received both gases twice			analysed by ANOVA #NCGC calculated

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

F.4.2 Prednisolone for the palliation of cough

Table 76: Hope-Gill 2003 [191]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Hope-Gill 2003 [191] Country of study: UK	Patient group: IPF patients with disabling cough (all had a visual analogue score	All patients Prednisolone 40-60 mg/day for least 4 weeks.	visual analogue scale score of cough intensity using a 10 cm scale	Baseline: 7.2±0.8 Post treatment: 2.2±2.5 p value: <0.05	Funding: supported by a grant from lechyd morgannwg health R&D consortium. Asta Zeneca pharmaceuticals donated the omeprazole used in this study.

Study details	Population	Methods	Outcome measures	Effect size	Comments
Study design: Prospective cohort Who was blinded: NR Setting: NR Duration of follow-up: 4 weeks	of 5 or more on a 10cm scale)* Inclusion criteria: Diagnosis of IPF based on ATS criteria Exclusion criteria: NR** Evidence of respiratory infection within 1 month History of smoking within 1 year Post nasal drip, rhinitis, or catarrhal symptoms Symptoms of gastroesophageal reflux Asthma or respiratory disease other than IPF Angiotensin inhibitor, bronchodilator, or no steroidal anti-inflammatory drug therapy Other major systemic illness. Airway hypersensitivity All patients	All subjects were asked to grade their cough severity from 0 (no cough) to 10 (disabling) using a 10 cm visual analogue scale.			Limitations: No baseline data provided Small sample size No comparison Method of blinding not reported Indirect intervention- prednisolone used to study the cough reflex to stimulants Additional outcomes: Cough response to capsaicin, substance P and bradykinin. Sputum cell counts, albumin & neutrophin measurements. Results of the above for patients not treated with steroids and healthy controls. Notes: *Main study looked at IPF patients vs. healthy control studying the cough response to capsaicin, substance P and bradykinin. An additional 6 patients where tested before and after steroid therapy. This table reports the results for the 6 patients treated with steroids. **The exclusion criteria is stated for patients in the main study Patients reported to have no difference in lung function tests between these patients and those from the main study not treated with steroids Baseline lung function results for patients in main study:

Study details	Population	Methods	Outcome measures	Effect size	Comments
	N: 6 Drop outs: 0				N=10 FVC % predicted: 77.43 TLC % predicted: 67.02 DLCO % predicted: 42.44

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

F.4.3 Thalidomide for the palliation of cough

Table 77: Horton 2008[192]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Horton 2008[192] Country of study: USA Study design: Prospective cohort Open label phase II trial Abstract Who was	Patient group: 11 patients with chronic cough Inclusion criteria: As above Exclusion criteria: NR All patients N:11 Drop outs: 5	All patients Thalidomide administered daily in 100-400mg doses. Patients were followed with interval histories, physical examinations and quality of life questionnaires.	Cough score	Baseline:4.9±0.3 Follow up at 3 months: 2.2±1.6 P = 0.03 (data from 6 patients for who there was complete data)	Funding: NR Limitations: Abstract Limited information given on methodology, no baseline data, and post treatment Large dropout rate Additional outcomes: quantification of cough was recorded by subjects on question 2 of SGRQ

Study details	Population	Methods	Outcome measures	Effect size	Comments
blinded: NR Setting: Hospital Duration of follow-up: 3 months					Side effects; most commonly reported adverse event was dizziness and constipation.

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 78: Horton 2012[193]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Horton 2012[193] Country of study: USA Study design: Double blind 2 treatment 2 period crossover trial	Patient group: Consecutive eligible patients between February 2008 and March 2011 Inclusion criteria: >50 years Clinical history consistent with IPF (symptom duration >3 months <5 years) chronic cough (defined by cough of more than 8 weeks duration that adversely affected QOL and was not due to identifiable causes)	All patients Patients received each treatment for 12 weeks in the crossover design with a 2 week washout period All patients began on 50mg of thalidomide orally at bedtime, the does was increased to 100mg if not improvement in cough was seen after 2 weeks*	QOL: cough quality of life questionnaire (mean±SD)	Baseline:60.5±12 Post treatment placebo:58.7±14.0 Post treatment thalidomide:47.2±13.4 Mean difference (95% CI):-11.4(-15.7to-7) P value:<0.001	Funding: Celgene corporation provided the study drug and funding but had no role in study design, conduct, analysis or manuscript Limitations: Treatment crossover was the washout period adequate Unclear allocation concealment
			QOL: Visual analogue scale (mean±SD)	Baseline:64.8±21.4 Post treatment placebo:61.9±26.5 Post treatment thalidomide: 32.2±26.1 Mean difference (95% CI):-31.2(-45.2to-17.2) P value:<0.001	

Study details	Population	Methods	Outcome measures	Effect size	Comments
Who was blinded: double blind study investigators and participants Setting: hospital Duration of follow-up: 12 weeks	HRCT consistent with IPF or SLB results confirming interstitial pneumonia FVC between 40-90%predicted TLC between 40-80% predicted DLCO between 80-90% predicted at screening Exclusion criteria: Pregnancy Female with childbearing potential Toxic or environmental exposure to respiratory irritants Collagen vascular disease Airflow obstruction Active narcotic antitussive use Peripheral vascular disease Neuropathy Inability to give informed consent Allergy or intolerance to thalidomide Life expectancy less than 6 months in the opinion of investigators All patients N: 24 Drop outs: 4(1 patient withdrew before receiving treatment, 3	All patients received sodium docusate 100mg orally during the trial for constipation and vitamin b complex supplement for any undiagnosied deficiency. Any prescription for cough was discountinued 2 weeks before the trial and no patients began benzonatate therapy or reported changes in ACEi/ARB GERD or sinus therapies during the trial.	SGRQ total (mean±SD)	Baseline:57.4±18.8 Post treatment placebo:56.9±17.1 Post treatment thalidomide: 43.9±16.0 Mean difference (95% CI):-11.7(-18.6to-4.8) P value:0.001	Small sample size Single centre study Short duration of study Additional outcomes: Adverse events Notes: Randomisation schedula prepared by using manual algorithm. A random seed number was generated by using RAND function in excel. The pharmacist dispensing the drug was the only person who had access to the treatment. • This happened in 21/22 patient's receiving thalidomide and all placebo patients
			SGRQ symptom domain (mean±SD)	Baseline:67.7±19.7 Post treatment placebo:62±18.3 Post treatment thalidomide: 50.3±20.9 Mean difference (95% CI):-12.1(-22.2to-2.0) P value:0.018	
			SGRQ impact domain (mean±SD)	Baseline:48.1±20.7 Post treatment placebo:49.0±19.4 Post treatment thalidomide:34.3±16.1 Mean difference (95% CI):-13.1 (-19.7to-6.6) P value:<0.001	
			SGRQ activity domain (mean±SD)	Baseline:64.3±22.7 Post treatment placebo:65.8±18.7 Post treatment thalidomide: 60.9±14.2 Mean difference (95% CI):-3.3(-9.8 to-3.2) P value:0.31	

Study details	Population	Methods	Outcome measures	Effect size	Comments
	withdrew after 2 weeks due to worsening health) M:F: 18:5 Age(mean):67.6±7.8 Previous cough treatment:8 (35%) GERD:12(52%) Therapy for GERD on entry in the study proton pump inhibitor: 10(43%) Chronic sinitis: 8(34%) ACEi/ARB use: 7(30%) FVC % predicted(mean±SD):70.4±13.7 TLCO% predicted(mean±SD):63.6±11.4 DLCO% predicted(mean±SD):57.4±14.4				

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 79: Saini 2011[418]

Study details	Population	Methods	Outcome measures	Effect size	Comments

Study details	Population	Methods	Outcome measures	Effect size	Comments
Saini 2011[418] Country of study: UK Study design: prospective cohort Who was blinded: NR Setting: hospital Duration of follow-up: NR	Patient group: 9 Patients referred to ILD clinic between 2009 -2011for assessment for their cough Inclusion criteria: Patients with IPF who had "significant cough"* Exclusion criteria: All patients N: 6 (4 IPF, 1 hypersensitivity pneumonitis, 1 fibrotic cryptogenic organising pneumonia) Drop outs: NR Male: 72% Age (mean (range)): 69 (51-88)	All patients Treated with thalidomide – no details of starting dosages given ("two patients are currently stable on 50mg once daily and 1 with 50mg alternate daily")*	Cough score: (Leicester cough questionnaire) Median (IQR)	Baseline (pre-thalidomide): 74.5(13.25) Post-treatment: 51.5(49.25) P=0.046	Funding: NR Limitations: Abstract limited information on methodology and results, baseline data, treatment and post treatment. All patients had been treated with other drugs for cough before starting thalidomide therapy, no washout period stated Additional outcomes: None Notes: *the 9 patients who were initially referred for assessment were assessed using a modified version of Leicester cough questionnaire in conjunction with subjective symptoms. A trail of PPI (omeprazole 40mg) and prednisolone 10mg for 6 weeks – two subjects were excluded as they did not have a significant cough and one patient declined thalidomide after initial screening. *3 patients stopped thalidomide subsequent to rash.

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

F.4.4 Morphine for the palliation of breathlessness

Table 80: Currow 2011 [93]

Study details	Population	Methods	Outcome measures	Effect size	Comments
Currow 2011 [93] Country of study: Australia Study design: Cohort. Phase II was an open-label prospective study Who was blinded: N/A Setting: outpatients from 4 tertiary university teaching hospitals in two states	Patient group: Patients with a palliative diagnosis (only ILD reported in this table). Recruited from 4 tertiary university hospitals between July 2007- October 2009. Inclusion criteria: Opioid-naïve Palliative diagnosis Age ≥ 18 years Ongoing dyspnoea (3 or 4 on the modified Medical Research Council [MMRC] Dyspnoea Scale) Any underlying reversible causes of dyspnoea must have been maximally treated On stable medications and oxygen (if required) for the seven days before commencing the study, with an estimated prognosis of > 1 month. Exclusion criteria: Regular use of any opioid medication in the 2 weeks before	All patients N= 10 3 week titration period. Received 10mg daily of sustained-release morphine sulphate, which was increased in non-responders by 10mg daily each week to a maximum of 30mg daily. Administered with laxatives (sodium docusate with sennnosides). The participant was withdrawn if there were unacceptable side effects or no response to maximum dose. Morning and evening dyspnoea VAS scores were recorded on days 5-7 of each seven-day week (i.e. during steady-state) were averaged and contributed to assessments of the number of people who responded to morphine and the dose at which they responded; an individual	VAS intensity of dyspnoea at baseline 100mm VAS scale "right now" (hence, at rest) anchored at 0mm as "no breathlessness" and at 100mm as "worst imaginable breathlessness". Participants recorded dyspnoea twice daily in a purpose-printed diary.	Baseline Average: 44.8 SD: 15.4 Range: 18-61 Difference- first and last measured VAS in Phase II Average: 3.2 SD: 32.7 Range: -33 to 46	Funding: National Health and Medical Research Council Limitations: Small sample size Additional outcomes: Improvement in dyspnoea (VAS scale) for COPD and cancer. Side effects Participant ranked 'physical symptoms or problems that have been the biggest problem for you over the past two days'(McGill Quality of life questionnaire) data not reported for ILD separately Indirect intervention results taken from phase II of a pharmacovigilance study

Study details	Population	Methods	Outcome measures	Effect size	Comments
of Australia Duration of follow-up: N/A	screening A true hypersensitivity reaction to opioids History of substance misuse Use of monoamine oxidase inhibitors in the last 2 weeks Functional status <50 on the Australian –modified Karnofsky Performance Scale (AKPS) A calculated creatinine clearance of <15mL/ min Pregnancy Confusion (< 24/30 on a Mini Mental State Examination) Unwilling/ unable to complete the study measures. All patients N: 83 (total), 10 ILD Drop outs: 4 (toxicity), 2 (other reason) 4 patients proceeded to Phase IV	improvement of 10% over baseline was considered, a priori, as a clinically significant improvement.			Notes: Phase II part of study only Study withdrawal initiated at any time by the participant. Other reason included AKPS falling below 30, sudden increase dyspnoea, or participant death.

Abbreviations: M/F=male/female, N=total number of people randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

F.5 Psychosocial support

Study details	Patients	Interventions	Outcome measures	Qualitative statement	Comments
Collard 2007[78] Country of study: Study design: Qualitative Questionnaire survey Who was blinded: None Setting: NR Duration of follow-up: NR	Patient group: Patients and careers of current and deceased for which address were available between July 2003 and December 2004 Inclusion criteria: NR Exclusion criteria: NR All patients N: 1448 Patients :1251 Caregivers: 197 Age (median): 65 Drop outs: 0	All patients A questionnaire survey* was distributed to over 2000 members, in both paper and via email with a link to a web based survey site. The survey was also made available to CPF** members online and in paper form through the CPF website, sponsored seminars and institutional partners. The completed surveys were compiled by Michaels Opinions Research Inc. Results from this publication are based on responses from living patients or caregivers of living patients. Two authors reviewed the raw data and directed the analysis	Education and resources	63% somewhat/ strongly agreed with the statements there was a clear lack of information and resources about PF 51.2% reported being generally/very well informed regarding the treatment options available at the present time. 38.7% reported being generally/very well informed regarding the benefits of pulmonary rehabilitation. 42.5% reported being generally/very well informed regarding the benefits of managing supplemental oxygen. 32.5% reported being generally/very well informed regarding the risks and benefits of lung transplantation.	Funding: DuBrul family Fund and the family of Helen and Michael Gavin Limitations: Sampling: self identified no confirmation of diagnosis, non probability sampling- sampling bias Generalisability – external validity Large proportion of non-responses- response rate 50% . Responder bias- responders may be substantially different to non-responders. Recall bias. Misinformation bias. Additional outcomes: Incorrect diagnosis's Experiences with diagnosis: procedures undertaken Experience with treatment: Types of treatments being received currently and in the past; prednisolone, cyclophosphamide,
			Experience with diagnosis	54.6% reported at least a 1 year delay between earliest indications of a potential breathing problem and the diagnosis of PF. 38.2% reported seeing 2 or more physicians before a diagnosis of PF was established 53.2% sought a second opinion 84.4% consulted a pulmonologist at some stage during their diagnostic evaluation	
			Experience with treatment	74.7% of respondents reported current pharmacologic therapy for PF Common reasons for not receiving	

Study details	Patients	Interventions	Outcome measures	Qualitative statement	Comments
	M/F: 54.3%/45.7%			pharmacologic therapy were; Fear of side effects 26% Ineffectiveness of therapy 23% No treatment prescribed 24% Early/stable disease 22% Respondents reporting use of herbs or nutritional supplements (24.4%) Oxygen use was reported by 61%, Pulmonary rehabilitation and physical therapy referrals were reported by a minority of patients (31.8% and 23.9%) Behavioural health counselling referrals were uncommonly reported 58.7% had transplantation discussed with them	azathioprine and colchicine, interferon gamma 1-b Notes: *survey was developed in conjunction with clinicians experienced in issues surrounding the management of pulmonary fibrosis in order it better understand the experiences of patients with this condition **Coalition for pulmonary fibrosis (CPF); is a non-profit organization founded to further patient and physician support and education, and to enhance research efforts in pulmonary fibrosis. The CPF is governed by pulmonologists, patients, investigators and advocacy organisations. Membership is free and most members learn of the CPF through seminars, word of mouth or the internet.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lindell 2010[285]	Patient group: university based ILD programme Inclusion criteria:	Group 1 Program to Reduce Idiopathic Pulmonary	* Dyspnoea (university of California at San	Group 1: 49.51±22.64 Group 2: 49.88±22.64 p value: 0.972	*Paper reports 'adjusted mean scores' for these

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Country of study: USA Study design: RCT (quantitatively driven concurrent nested mixed-method design) Who was blinded: no-one Setting: Centre for Interstitial Lung Disease, University of Pittsburgh medical centre Duration of follow-up:	Patients: age >21 years able to read and understand English diagnosis of IPF have an FVC reflecting moderate (FVC 55%-70% predicted) or severe (FVC <55% predicted) disease Care partners: Age >21 years Able to read and understand English Lives with or cares for the patient with IPF Exclusion criteria: NR All patients N: 42 Drop outs: 2 patients and 3 care partners Group 1 N: 10 Age (mean): 65.2±10.28 % male: 33.33% Diagnosis: Biopsy: 14.29% HRCT: 33.33%	Fibrosis Symptoms and Improve Management (PRISIM) intervention 6 weekly group sessions attended by patients and care partners. The content for these sessions was developed by a pulmonary clinical nurse specialist, a psychiatric clinical specialist with training as a cognitive behavioural therapist and an advanced care planning instructor. Group 2 usual care only Patients were seen by members of the clinical care team consisting of a pulmonary clinical nurse specialist and physicians with expertise in the management of IPF, typically at intervals of every3 to 6 months. The pulmonary clinical nurse specialist was available by phone to answer questions and	Diego Shortness of breath Questionnaire): 6 point scale where 0=not at all to 5=maximal or unable to do) during 21 activities of daily living associated with varying exertion. Total score out of 120		outcomes- raw data not reported therefore unable to meta-analyse Funding: Fairbanks-Horix Foundation Limitations: Reporting of outcomes: pre scores reported more fully than post treatment scores (graphical data only) Small sample size Discrepancy in method of diagnosis between the two groups- ATS/ERS criteria not used Additional outcomes: Care partner outcomes for anxiety, depression, perceived stress and SF-36 physical and mental. SF-36 physical and
			*Anxiety (Beck Anxiety Inventory): a standardised 21 item tool that uses a 4 point scale (0=absent/not at all disturbing to 3= I could barely stand it). Total score ranged from 0-63. 0-7= no anxiety, 8-15= mild anxiety, 16-25= moderate anxiety, >26= severe anxiety	Group1:15.13±6.92 Group 2:8.56±6.95 p value: 0.077	
			*Depression (Beck Depression Inventory-II), a 21 item validated self-report instrument designed to measure the severity of depression in adults	Group1: 9.71±4.43 Group 2: 9.44±4.35 p value: 0.894	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	FVC>55%: 40% FVC 50-55%: 5% FVC <50%: 5% Current or prior depression: 9.52% Drop outs: 0 Group 2 N: 11 Age (mean): % male: 42.9% Diagnosis: Biopsy: 42.86% HRCT: 9.52% FVC>55%: 30% FVC 50-55%: 10% FVC <50%: 10% Current or prior depression: 9.52% Drop outs: 4.76%	conducted a monthly support group for those wanting to attend. Psychologic counselling was provided if indicated but was not offered on a routine basis	and adolescents aged 13 and over. a score of 0-13= minimal depression, 14-19= mild depression, 20-28= moderate depression, 29-63= severe depression.		mental domains (totals not given) Qualitative outcomes (interviews) Notes: Randomisation: permuted block design Pilot study therefore sample size not based on a power calculation
			*Perceived stress-designed to measure the degree to which subjects find their lives unpredictable, uncontrollable and overloading. Total scores range from 0 to 40 with higher scores indicating more stress.	Group1:19.32±3.64 Group 2: 18.20±3.65 p value: 0.531	
			Qualitative analysis		

Study details	Patients	Interventions	Outcome measures	Qualitative statement	Comments
Shoenheit 2011[426]	Patient group: Patients with a physician-	All patients Patients participated in an in-depth interview conducted by a	Diagnostic pathway	58% (26 of 45) of patients reported 'protracted route' to confirmed diagnosis was characterized by an initial dismissal of the presenting symptoms, with repeated	Doxa Pharma S.r.l. was commissioned to execute the research protocol, which was conducted in accordance with the

Study details	Patients	Interventions	Outcome measures	Qualitative statement	Comments
Country of study: Germany, France, Italy, Spain, and the United Kingdom. Study design: qualitative in-depth interviews Who was blinded: None Setting: Patients home Duration of follow-up: N/A	confirmed diagnosis of IPF Inclusion criteria: As above Exclusion criteria: NR All patients N: 45 Age (median): 67 Drop outs: 0 M/F: 22/23	trained facilitator. Whenever possible, the caregivers were encouraged to participate as well. Whenever possible, the caregivers were encouraged to participate as well (care givers participated in 18 [40%] of the 45 interviews). All interviews were performed in the respondents' homes and typically lasted for 1 hour in length or longer. The interviews were conducted using a qualitative discussion guide*; participants were asked to recount their IPF-related health care experience in an open and free-ranging manner. The interviews were structured to include two projective techniques: an associative technique, whereby respondents are asked to select images that express their feelings; and a constructive technique in which respondents are asked to recall what was said in a particular situation such as the moment that the diagnosis was communicated** Informed consent was obtained from each subject and family member prior to the interview.		physician for further evaluation and testing. This was commonly interrupted by an 'acute event,' which was often initially attributed to other causes this frequently resulted in an emergency room visit and subsequent hospitalization, where a detailed evaluation by a pulmonologist would eventually result in a diagnosis of IPF. This process reportedly took as long as 2–12 years, despite repeated visits to health care practitioners during this period. Patients who were subjected to this protracted route to diagnosis were often critical of the care they received, citing both a lack of empathy and emotional support and an apparent lack of competence among health care practitioners. There was a tendency among these patients to perceive the initial diagnosis not as a working hypothesis but rather as an erroneous or missed diagnosis. In a minority of cases (16%), the diagnosis was made within a month of the patient's initial presentation. Early detection was attributed to a well-informed patient researching their symptoms online, a well-informed physician detecting the distinctive 'Velcro1 rales' on chest auscultation, which prompted further evaluation for possible interstitial lung disease, or routine surveillance of known drug toxicities (e.g.	International Chamber of Commerce (ICC)/The European Society for Opinion and Market Research (ESCOMAR) International Code on Market and Social Research and other ESOMAR/ European Pharmaceutical Market Research Association (EphMRA) professional standards. Data was processed in accordance with Legislative Decree No.196 (30 June 2003), as well as the ESOMAR Standards and the 'Code of Ethics and Conduct' issued by the Guarantor of Privacy (16 June 2004). Funding: InterMune Limitations: IPF diagnosis wasn't confirmed using current criteria Recall bias Small sample size Generalisability Additional outcomes: demographics

Study details	Patients	Interventions	Outcome measures	Qualitative statement	Comments
		Audio recordings were made during each of these interviews and used to assist with accurate and thorough data capture and analysis. Audio recordings of the interviews were transcribed and all individual data were then collated in content analysis grids with data from other respondents and presented in aggregate with complete confidentiality maintained for each participant. Researchers from all five counties analyzed the raw data in a collaborative process aimed at identifying the primary themes emerging from the results of the survey. At the onset of each interview, the moderator read a scripted introduction that described the purpose and nature of the discussion as follows: 'The overall purpose of this discussion is to understand how your IPF is managed, and what your current needs are. The discussion will take the form of an interactive session, with exercises/ tasks which are designed to be enjoyable as well as informative for us; they allow us to		amiodarone).	most commonly reported presenting symptoms median time from initial presentation and diagnosis number of physicians consulted before receiving a confirmed diagnosis patients expectations of available treatments commonly reported misdiagnoses Notes: *The discussion guide was developed after a comprehensive review of the limited relevant medical literature and with input from health care practitioners with expertise in IPF. ** The choices of images and the output of the constructive task were not considered to have any interpretive value except in the context of what the respondents verbalized on completion of the task.
			Diagnosis	"Patients expressed a dissatisfaction with the manner in which the diagnosis was divulged, citing insensitivity on the part of the health care practitioner and insufficient time during the consultation to address the full range of patients' questions and concerns"	
			Quality of care in tertiary centre	"Patients treated in a tertiary care center consistently reported greater satisfaction with the quality of care, the availability of treatment options (including enrolment in a clinical trial), the knowledge and expertise of health care practitioners, and the frequency of follow-up visits and routine monitoring. Additionally, patients treated in a tertiary care center commonly reported that the opportunity to interact with other IPF patients provided important benefits, including psychological support and practical disease management tips"	
			Quality of care in community practice	"Patients treated in the community practice setting consistently reported infrequent follow-up visits (typically once per year), short duration of visits (generally less than 10 minutes), and a lack of available treatment options. In general, these patients were less well informed about their disease and the available treatment options, including pulmonary rehabilitation, lung transplantation, and	

Study details	Patients	Interventions	Outcome measures	Qualitative statement	Comments
		access information that we would not be able to access by asking a straight question. In particular, we are interested in understanding not just what you think but why you think it.' Because of the exploratory nature of the research objectives, wherever possible, attempts were made to elicit spontaneous responses, with prompts being used only as necessary to advance the discussion and to glean the study elements of interest.		enrolment in a clinical trial"	
			Patients aims for disease management	"Focused on disease stability and efforts to slow progression if feasible. For only a small minority of those surveyed, the emphasis was either on lung transplantation as the 'hope' for future survival beyond IPF, or some belief that their particular condition was atypical and associated with a less dire prognosis"	
			Commonly reported unmet medical needs	Improved access to Centres of Excellence Clear and understandable disease education resources Comprehensive family support/counselling programs Fewer bureaucratic barriers to scheduling specialist appointments and obtaining supplemental oxygen Patient advocacy and public education improved diagnostic techniques more effective treatment options	
			IPF on Patients' Quality of Life and Emotional Well-Being	personal independence Loss of independence that coincided with the deterioration in health and inability to perform routine daily tasks. The requirement for supplemental oxygen was commonly identified as a milestone in the patients' loss of independence, as it is at this point that the disease becomes highly visible to others and excursions outside the	

Study details	Patients	Interventions	Outcome measures	Qualitative statement	Comments
				home begin to require significant logistical planning. In many cases, this loss of independence has a notable impact on the patient's emotional well-being, as they begin to perceive themselves as a burden to both their family and society relationships with others considerable difficulty in continuing relationships with friends and acquaintances due to their worsening pulmonary status and immobility, as well as a general lack of awareness and understanding of the disease financial status 20% of respondents reported financial difficulties as a result of their inability to work and the consequent reduction in income. This further served as a stressor, as well as the concern that they were now an increasing burden to their families and loved ones	

F.6 Pharmacological interventions

F.6.1 Warfarin vs. Placebo

Table 81: Noth 2012[359]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Noth 2012[359] Comparison: Warfarin versus placebo Setting: Multicentre trial; 22 centres in the USA Duration of follow-up: 48 weeks planned: Study was stopped by Independent safety and monitoring board with a mean follow up of 28 weeks Design: Parallel group	Patient group: Patients aged 35 to 80 meeting ATS/ERS diagnostic criteria for IPF Inclusion criteria: Progressive IPF patients i.e. those with a history of 1) worsening dyspnoea or 2) physiologic deterioration defined as an absolute of either FVC ≥ 10% or DLCO ≥ 15%, progression of radiographic findings a reduction is SaO2 of ≥ 5%. Patients must be willing to do home INR testing. Exclusion criteria: Current indication for or treatment with warfarin, prasugrel, or clopidogrel combined with aspirin; presence of an increased	Group 1: (n=72) Oral warfarin dose adjusted to maintain an INR of 2-3 Group 2: (n=73) Sham dose adjusted placebo	All-cause mortality at trial stop (RR)	Group 1: 14 Group 2: 3 RR [95%CI]: 4.73 [1.42, 15.77] p=0.01	Funding: Unclear Limitations: All disclosures on online appendix and not presented in paper High risk of attrition bias as trial stopped prior to completion for safety thus all available results analysed together and high overall dropout rate Additional outcomes: Plasma D-Dimer levels
			Combined all-cause mortality and non-elective non bleeding hospitalisations at trial stop (RR)	Group 1: 21 Group 2: 10 RR [95%CI]: 2.13 [1.08, 4.20] p=0.03	
			Respiratory cause mortality at trial end (RR)	Group 1: 11 Group 2: 3 RR [95%CI]: 3.72 [1.08, 12.77] p=0.04	
			Cardiac cause mortality at trial end (RR)	Group 1: 3 Group 2: 0 NS difference	
			All-cause mortality at trial stop (HR)	HR: 4.85 SE:	
			Combined all-cause mortality and non-	HR:2.12	

	risk of bleeding; a recent CVA or GI bleed; any signs and symptoms of a severe, progressive or uncontrolled comorbid illness; presence on active list for lung transplantation. All patients N:145 Age (mean): 67 Male/female (%): 63/27 Mean predicted FVC (%): 59 Mean predicted DLCO (%): 34 Drop outs: Group 1: N: 72 Age (mean): 67.3 +/- 7.1 Male/female (%): 67/33 FVC, % predicted (mean +/- SD): 58.9 +/- 16.2 DLCO % predicted (mean +/- SD): 33.8 +/- 12.4 Drop outs: Group 2: N: 73 Age (mean): 66.7 +/- 7.4		elective non bleeding hospitalisations at trial stop (HR)	SE:	Notes:
			Change in 6MWD (m),FVC (%) and DLCO (%)at 48 weeks (extrapolated)	Non-significant difference between groups reported in text narrative. No data given	
			QoL	Non-significant between groups reported in text narrative. No data given	
			Number of participants with IPF exacerbations at trial end	Group 1: 6 Group 2: 2 Non-significant difference	
			Number of participants with major bleeds at trial end	Group 1: 2 Group 2: 1 Non-significant difference	
			Number of participants with minor bleeds at trial end	Group 1: 6 Group 2: 2 Non-significant difference	
			1 and 3 year survival rate	NR	
			Hospitalisations due to IPF	NR	
			Dyspnoea	NR	

	Male/female (%): 79/21 FVC, % predicted (mean +/- SD): 58.7 +/- 16.1 DLCO % predicted (mean +/- SD): 34.6 +/-13.4 Drop outs: NS differences in baseline populations				

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood , DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

F.6.2 Warfarin & prednisolone vs. Prednisolone

Table 82: Kubo 2005[257]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Kubo 2005[257] Comparison Warfarin + oral prednisolone vs oral prednisolone Setting: Hospitalised patients Duration of follow-up: 3 years?	Patient group: Patients with diagnosis of IPF admitted to hospital Inclusion criteria: diagnosis of IPF, deterioration of IPF to varying degrees despite conventional treatment without prednisolone, non-smoker Exclusion criteria: clinical or serological evidence of	Group 1- anticoagulant group Oral prednisolone + oral warfarin Oral prednisolone administered same schedule as group 2 Oral warfarin was administered such that the INR value was maintained between 2-3. Group 2	Mortality	Group1: 5/23 Group 2: 20/33 p value: 0.6	Funding: NR Limitations: -allocation concealment NR - large dropout rate from intervention group: 6 withdrew because they were afraid of side effects and disliked the extra blood tests
			Hospitalisations due to IPF (acute?) exacerbations Denominator= number of hospitalisations	Group1: 11/15 Group 2: 21/29 p value: NR	
			1 year survival rates	Group1: 87% 29/30 (97%) Group 2: 58% 13/23 (57%) p value: (If no p-value:	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	collagen vascular disease, history of exposure to fibrogenic agents, active infection, malignancy, haemoptysis, hypersensitive pneumonitis, GI bleeding, or ARDS. Obvious signs of existing PE, pulmonary hypertension due to pulmonary thromboembolism, or phlebitis by colour Doppler ultrasonography or enhanced CT All patients N: 56 Age (mean): 69.4 (47-89) Drop outs: Group 1-anticoagulant N: 31 Age (mean): 71.3 (10.6) Drop outs: 8 Male/female:14/9 Method of diagnosis: -open lung biopsy:4 -transbronchial biopsy: 8 -HRCT: 23	Oral prednisolone 0.5 – 1.0 mg/kg/d for 4 weeks, subsequent tapering of dose to 10 – 20 mg/day over a 1 month period.		Sig/Not sig/NR)	-Not double blind? -all participants non-smokers (IPF associated with smoking) -hospitalised patients- bias towards acutely ill or deteriorating patients- high % of exacerbations, short median survival -no patient group treated with anticoagulant alone Additional outcomes: -plasma d-dimer HR for death in non-anticoagulant group compared to anticoagulant group 2.9 (1.0 -8.0) p=0.04 -number of re-hospitalisations -cause of re-hospitalisations -rehospitalisation free period
			3 year survival rates	Group1: 63% (21/30) Group 2: 35% (8/23) p value: NR	
			Lung capacity	NR	
			Gas transfer	NR	
			Health-related QoL	NR	
			Adverse events	NR	
			Dyspnoea	NR	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	Clinical condition: -hugh jones score: 3.3 (0.5) -need for supplemental oxygen:11 Pulmonary function: -%FVC: 70 (10) -PaO2: 69 (13) -DLCO, % predicted: 59 (15) - Plasma d-dimer:2.1 (1.6) Group 2 N: 33 Age (mean): 68.1 (9.7) Drop outs: Male/female: 17/16 Method of diagnosis: -open lung biopsy:5 -transbronchial biopsy: 12 -HRCT: 13 Clinical condition: -hugh jones score:3 (1) -need for supplemental oxygen:11 Pulmonary function: -%FVC:71 (17) -PaO2:73(9) -DLCO, % predicted: 63				Notes: -diagnosis of IPF determined previously by histologic evaluation of open lung biopsy or transbronchial lung biopsy specimens or radiologic evaluation using HRCT, or both. Diagnosis by radiologist blinded - random number tables for randomisation

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	(14) -Plasma d-dimer:1.9 (1.3)				

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood , DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

F.6.3 Sildenafil vs. Placebo

Table 83: Jackson 2010[207]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Jackson 2010[207] Country of study: USA Study design: single-centre, double blind, placebo-controlled trial (RCT) Who was blinded: Treatment assignments	Patient group: Typical patients with IPF, who fulfilled the clinical diagnostic criteria of the American Thoracic and European Respiratory Societies. Subjects recruited from August 2006 to November 2008. Inclusion criteria: • IPF onset between 3 -36 months before screening • Diagnosis must be made by HRCT scan showing definite / probable IPF and VATS lung biopsy showing definite/ probable UIP • RVSP or PAsys 25–50 mmHg, based on echocardiography and absence of decompensated right heart failure (NYHA class I or II acceptable) • Age 21 -85 years, inclusive. Patients aged 21–40 years must have diagnosis by open or video-assisted thoracoscopic surgery lung biopsy	Group 1 Subjects were treated with sildenafil citrate tablets orally in an escalating dose schedule: 20 mg daily for 3 days, 20 mg twice daily for 3 days, and then 20 mg three times daily for the remainder of the trial. Patients took the study drug at home after receiving verbal and written	6MWD: metres (Approximation read off graph) (Mean ±SD)	Group1: 330 ±40 Group 2: 355±80 Relative risk [95% CI]: NR p value: NR	Funding: Supported by a grant from the Veterans Administration Research Service. Pfizer UK provided sildenafil and placebo donation. Limitations: • Unclear allocation concealment • Small sample size • Study of short duration • 21.4% drop out rate in placebo arm
			Lung capacity FVC (% of predicted value) (mean change ± SD)	Group1: -4 ± 14.2 Group 2: -5.3 ± 9.8 Relative risk [95% CI]: NR p value: 0.79	
			Gas transfer DLCO (% of predicted value) (mean change ± SD)	Group1: -6.1 ± 10.6 Group 2: -2.5 ± 8.4 Relative risk [95% CI]: NR p value: 0.341	
			Dyspnoea: 10 point Borg scale (after exercise stress test)	Group1: 4.3±1.5 Group 2: 3.6±1.6 Relative risk [95%	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
and personnel Setting: Clinical Duration of follow-up: 6 months	• FVC 40–90% predicted or DLCO 30–90% predicted or impaired gas exchange with rest or exercise • 6MWT (distance) ≥150 m and ≤500 m • Worsening of one of the following in the last year :>10% decrease in percent predicted FVC or worsening dyspnoea at rest/ on exertion • Ability to understand and sign a written informed consent form and comply with the requirements of the study • Absence of clinical features suggesting infection, neoplasm, sarcoidosis, collagen-vascular disease or exposure to known fibrogenic environmental factors Exclusion criteria: • PAsys>50 mmHg, based on echocardiography or TR velocity≥ 3.2 m/s • Severe heart failure (NYHA class III or IV or LVEF<25%) • 6MWD <150 m />500 m • FEV1/FC ratio <0.5 at screening (post-bronchodilator) • Residual volume>120% predicted • Any condition other than IPF likely to result in the death of the patient within 2 years • History of unstable or deteriorating cardiac or neurologic disease • Pregnancy or lactation.	instruction Group 2 Identical placebo	(Mean ±SD)	CI]:NR p value: 0.202	Additional outcomes: • Exercise stress test times before and after intervention. • PFTs; TLC, RVSP, SaO2 Notes: Randomly assigned, in a ratio as close as 1:1 as possible, used blocked randomization, with varying size of the blocks Double blind. Active and placebo compounds were identically packaged and labelled. Study personnel involved in obtaining 6MWT were blinded to adverse events, symptoms, and possible side effects. Treatment assignments were unblinded only at the completion of the
			Adverse events: chest pain	Group1: 1/14 Group 2: 0/15 Relative risk [95% CI]:NR p value: NR	
			Adverse events: facial flushing	Group1: 1/14 Group 2: 1/15 Relative risk [95% CI]:NR p value: NR	
			Adverse events: visual disturbance	Group1: 1/14 Group 2: 0/15 Relative risk [95% CI]:NR p value: NR	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	• Current treatment with corticosteroids (oral or inhaled), Cytoxan, azathioprine, 247nblended247s, pirfenidone, interferon gamma or beta, anti-tumour necrosis factor therapy, or with endothelin receptor blockers. There must be at least 4 weeks of treatment washout before inclusion in this study • Investigational therapy for any indication within 28 days before treatment • Creatinine>1.5 9 upper limit of normal at screening • WBC<2,500/mm3 or neutrophil count<1500, hematocrit<30% or>59%, platelets<100,000/mm3 at screening • Total bilirubin >2.0 X upper limit of normal; aspartate or alanine aminotransferases (AST, SGOT or ALT, SGPT) >3 X upper limit of normal; alkaline phosphatise>3 X upper limit of normal; albumin <3.0 mg/dl at screening • Degenerative arthritis, cerebrovascular accident, or other limitation to mobility preventing completion of the 6MWT • Oxygen saturation on room air<80% at rest All patients N: 29 Age (mean): NR Drop outs: 4 Group 1				study. Statistical analyses were performed on intent-to treat basis. All statistical tests were two-sided tests at a nominal 5% level of significance. Drug compliance ranged from 89%-100%.for the sildenafil and placebo groups respectively

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	N: 14 Age (mean): 70 ± 12.1 Drop outs: 3 Baseline 6MWD (mean ±SD): 333.9 ± 68.8 Predicted FVC (mean ±SD): 62.2 ± 16.7 Predicted DLCO (mean ±SD): 40.4 ± 7.9 Borg dyspnoea scores (after exercise stress test)(mean ±SD): 3.6±1.6 Group 2 N: 15 Age (mean± SD): 71 ± 6.2 Drop outs: 1 Baseline 6MWD (mean ±SD): 358.8 ± 72.2 Predicted FVC (mean ±SD): 62.7 ± 10.3 Predicted DLCO (mean ±SD): 43.5 ± 9.4 Borg dyspnoea scores (after exercise stress test) (mean ±SD): 4.1 ±2.1				

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood , DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

Table 84: Zisman 2010[512]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Zisman 2010[512] Country of	Patient group: Diagnosed with advanced IPF according to consensus criteria*	Period 1 Group 1 20 mg of sildenafil 3 times a day, daily	6MWD: Improvement in the 6-minute walk distance of	Group1: 9/89 (10%) Group 2: 6/91 (7%) Relative risk [95% CI]:NR	Funding: National Heart, Lung and Blood Institute (NHLBI) Cowlin Fund at the Chicago community

Study details	Patients	Methods	Outcome measures	Effect size	Comments
study: USA Study design: Multi-center, randomized, double-blind, placebo-controlled period (period 1), followed by open-label period (period 2). Who was blinded: Double - blind Setting: Clinical 14 IPFnet centres Duration of follow-up: 12 weeks	Inclusion criteria: Diagnosis of IPF, as defined by consensus criteria*, in an advanced stage, which was defined as a diffusing capacity for carbon monoxide of <35% of the predicted value. Exclusion criteria: • 6MWD <50m (164 ft) • A difference of more than 15% in the 6MWD between two pre-randomization walks; • Extent of emphysema greater than the extent of fibrotic change, determined by HRCT; • Treatment with medications containing nitrates • The presence of aortic stenosis/ idiopathic hypertrophic subaortic stenosis; • The initiation of pulmonary rehabilitation within 30 days after screening; • The initiation or change in the dose of any investigational treatment for idiopathic pulmonary fibrosis within 30 days after screening; • Treatment for pulmonary hypertension with prostaglandins, endothelin-1 antagonists, or other	for 12 weeks, then 20 mg of sildenafil 3 times a day, daily for 12 weeks Group 2 matched placebo Period 2 All subjects took part in a second 12-week open-label phase of the protocol once they had completed the first period. This second study period assigned all subjects to sildenafil 20 mg 3 times daily and evaluated the short-term effects of treatment and longer-term (24-week) safety profile	20% or more over baseline	p value: 0.39	Trust Pfizer (donated sildenafil and matching placebo) Masimo (donated pulse oximeters) Limitations: • Blinding not reported • Findings are applicable only to patients with advanced idiopathic pulmonary fibrosis • Unknown whether the treatment effect was driven by a particular subgroup of patients (e.g., those with more severe pulmonary vascular disease) • Small sample size • Study of short duration • improvements in subjective outcomes, such as quality of life, may be due to incomplete masking • SD have not been reported for all outcomes Additional outcomes: • PFT; partial pressure of oxygen, partial pressure of carbon dioxide, alveolar-arterial gradient, arterial oxygen saturation. • Acute exacerbations • Quality of life: SF-36
			Dyspnoea: Shortness of breath questionnaire – mean change (95% CI) (higher score indicates worse function)	Group1: 0.22 (-3.10 to 3.54) SD: 15.76* Group 2: 6.81 (3.53 to 10.08) SD: 17.45* #Absolute difference: -6.58 (-11.25 to -1.92) p value: 0.006	
			Dyspnoea: Score on Borg Dyspnoea Index after walk test- mean change (95% CI) (higher score indicates worse function)	Group1: 0.04(-0.30 to 0.37) SD: 1.76* Group 2: 0.37(0.04 to 0.70) SD: 1.58* #Absolute difference:-0.34 (-0.81 to 0.14) p value: 0.16	
			Quality of life: St Georges Respiratory Questionnaire, total score – mean change (95% CI) (higher score indicates worse function)	Group1: -1.64 (-3.91 to 0.64) SD: 10.8* Group 2: 2.45 (0.17 to 4.72) SD: 10.92* #Absolute difference: -4.08 (-7.30 to -0.86) p value: 0.01	
			Quality of life: EQ-5D self-	Group1: −0.01 (−0.06 to 0.03)	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	phosphodiesterase inhibitors within 30 days after screening; • A resting SpO2 < 92% while breathing 6 litres of supplemental oxygen; • Listed for lung transplantation All patients N: 180 Age (mean): 69 Drop outs: 14 M/F: 83%/17% Baseline 6MWD (mean): 265m Predicted FVC (mean): 56.8% Predicted DLCO (mean):26.3% Group 1 N: 89 Age (mean): 69.76 ± 8.71 Drop outs: 8 (4 adverse event 2 died 2 lost to follow up) M/F: 73 (82%)/16(18%) Baseline 6MWD (mean): 246.39m ±103.40m Predicted FVC (mean): 54.89% ±14.00% Predicted DLCO (mean): 25.81% ±6.03% Group 2		report questionnaire mean change (95% CI)	Group 2: −0.03 (−0.08 to 0.01) #Absolute difference: 0.02 (−0.04 to 0.08) p value: 0.54	• Quality of life: EQ-5D visual-analogue scale Notes: Supplementary Appendix: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1002110/suppl_file/nejmoa1002110_appendix.pdf Randomisation: 1:1 with the use of a permuted block design, with stratification according to clinical centre. Calculations based on chi squared test of equal proportions Intention to treat analysis - patients were deemed to have had no response if the rate of improvement was less than 20% at 12 weeks or if they died, withdrew from the study, or had missing data All P values are two-sided, and no adjustment has been made for multiple comparisons *Consensus criteria: The presence of all major criteria and 3 of the 4 minor criteria are required to meet study criteria for the diagnosis of IPF. Major Criteria 1. Clinical: exclusion of other known causes
			Lung capacity: FVC (% of predicted value) –mean change (95% CI)	Group1: -0.97 (-2.00 to 0.06) SD: 4.89* Group 2: -1.29 (-2.30 to -0.28) SD:4.85* #Absolute difference:0.32 (-1.12 to 1.76) p value: 0.66	
			Gas transfer DLCO (% of predicted value)–mean change (95% CI)	Group1: -0.33 (-1.36 to 0.71) SD: 4.91* Group 2: -1.86 (-2.91 to -0.83) SD: 4.99* #Absolute difference: 1.55 (0.08 to 3.01) p value: 0.04	
			Mortality (Death from any cause)	Group1: 2/89 (2%) Group 2: 4/91 (4%) Relative risk [95% CI]: NR	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	N: 91 Age (mean): 68.20 ± 9.25 Drop outs: 6 (4 adverse events 1, died, 1 underwent lung transplantation) M/F: 77(84%)/14(16%) Baseline 6MWD (mean): 269.55m ±129.83m Predicted FVC (mean): 58.73% ±14.12% Predicted DLCO (mean): 26.73% ±6.16%		Adverse events (all adverse events classed as 'serious'): coronary artery disease	p value: 0.43 Group1: 0/89(0%) Group 2: 1/91 (1.1%) Relative risk [95% CI]:NR p value: NR	(connective tissue diseases, environmental and drug exposures) of ILD 2. Physiologic: restriction on pulmonary function testing (PFT) and/or evidence of impaired gas exchange (decreased DLCO or increased alveolar-arterial partial pressure of oxygen difference [A-aPO2] at rest or with exercise) 3. Radiographic: HRCT with bibasilar reticular abnormality and honeycomb change with minimal ground glass opacities Minor Criteria 1. Age > 50 years 2. Insidious onset of unexplained dyspnoea 3. Duration of illness for ≥ 3 months 4. Bibasilar, inspiratory crackles # Absolute difference: this value is the absolute difference between sildenafil group and the placebo group in the change from baseline *Calculated by NCGC

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood , DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

F.6.4 Bosentan vs. Placebo

Table 85: KING2008A[239]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
KING2008A [239] Country of study: International Europe; Germany, France, UK, Italy Switzerland. USA, Canada and Israel Study design: RCT International prospective double blind randomised placebo-controlled, parallel group study Who was blinded:	Patient group: Patients with proven diagnosis of IPF Inclusion criteria: • Patients with proven diagnosis of IPF made within the last 3 years before enrolment according to ATS/ERS consensus guidelines (2000/2002). • In addition to clinical evaluation HRCT scan within the previous 3 months was used to give definitive diagnosis however if this couldn't be confirmed with HRCT a lung biopsy was mandatory to confirm histopathological diagnosis of UIP • Duration of illness 3 months or more • Baseline 6MWD between 150-499m Exclusion criteria: • ILD due to conditions other than IPF, • Severe restrictive lung disease (FVC <50% predicted, DLCO, corrected for haemoglobin level < 30% predicted, or RV ≥120%), • Obstructive lung disease (FEV1/FVC<65%), echocardiographic evidence of severe pulmonary hypertension (systolic pulmonary pressure ≥50 mm Hg or tricuspid	Group 1 Oral bosentan 62.5mg twice daily for 4 weeks, untitrated to bosentan 125mg twice daily thereafter (target dose) Patients unable to tolerate the target dose could be maintained on bosentan 62.5mg twice daily. Group 2 matching placebo	Exercise capacity 6MWT (Mean change in m from baseline up to 12 months ±SD)	Group1: -52± 121 Group 2: -34 ± 127 Relative risk [95% CI]:NR p value: 0.226	Funding: Supported by Actelion Pharmaceuticals Ltd, Allschwil, Switzerland Limitations: Allocation concealment unclear These results include data on patients who did not complete 12 months of treatment and for whom either a last observation carried forward or an imputed value of zero was used in the analysis Additional outcomes: Time to disease progression or death up to Month 12. Changes in PFT scores at month 12, categorised in to
			Dyspnoea scores Transition Dyspnoea Index	Group1: -1.7 Group 2: -2.6 Relative risk [95% CI]: NR p value: 0.292	
			Quality of life: St Georges Respiratory Questionnaire, total score – At 6 months 12 month data not shown – "differences continued to favour bosentan but were smaller"	Group1: 45.0 ± 21.3 Group 2: 47.8 ± 21.7 Relative risk [95% CI]:NR p value: 0.034	
			Lung capacity FVC (% of predicted value) (Mean absolute change from baseline up to 12 months)	Group1: -6.4 Group 2: -7.7 Relative risk [95% CI]: NR p value: NR	
			Gas transfer DLCO (% of predicted	Group1: -4.3 Group 2: -5.8	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Setting: Clinical Duration of follow-up: 12 months	regurgitation velocity ≥ 3.2m/s), • Severe congestive heart failure, or a terminal (expected survival <1 yr) concomitant illness. FVC of 90% predicted or resting Pao2 of less than 55 mmHg (sea level) or 50 mmHg (above 1,400m), • Haemoglobin concentration less than 75% of the lower limit of normal, • Systolic blood pressure less than 85 mmHg, • 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 corticosteroid therapy of 15 mg or less of prednisone or equivalent. Other prohibited drugs: Calcineurin inhibitors fluconazole and glyburide, due to potential interactions with bosentan. All patients N:154 Age (mean ±SD): Drop outs: 45 M/F: 112(73%)/42 (27%) Group 1 N: 71 Age (mean ±SD): 65.3 ± 8.4 Drop outs: 22		value) (Mean absolute change from baseline up to 12 months) Adverse events: abnormal LFTs	Relative risk [95% CI]: NR p value: NR Group1: 9/74 (12.2%) Group 2: 0/84 (0%) Relative risk [95% CI]:NR p value: NR	worsened and improved Notes: Within 4 weeks of screening eligible patients were randomised 1:1 Patients completing 12 months of double blind therapy continued treatment until the end of the study. Which was when the last patient randomised to study medication and not prematurely discontinued completed a full 12 months of treatment.

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	M/F: 49 (69%)/22 (31%) Baseline 6MWD (mean ±SD): 375 ± 92 Predicted FVC (mean ±SD): 65.9 ±10.5 Predicted DLCO (mean ±SD): 42.3 ± 9.5 Group 2 N: 83 Age (mean ±SD): 65.1 ± 9.1 Drop outs: 23 M/F: 63 (76%)/20 (24%) Baseline 6MWD (mean ±SD): 372 ± 74 Predicted FVC (mean ±SD): 69.5 ± 12.6 Predicted DLCO (mean ±SD): 41.4 ± 9.5				

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

Table 86: King 2011[242]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
King 2011[242] Country of study: Australia, Canada, Israel, Japan, South Korea, the United States, and	Patient group: As below Inclusion criteria: men and women aged 18 years or older with a proven diagnosis of IPF according to the American Thoracic Society/ European Respiratory Society	Group 1 Patients received an initial dose of 62.5 mg twice daily, up-titrated after 4 weeks to a target dose of 125 mg twice daily (or remaining at 62.5 mg twice daily if body weight < 40 kg). Patients unable to	QOL: SF-36 General health perceptions	Group1 :n=376 Baseline: 52.1 ± 21.5 1 year: 47.4 ± 24.1 Group 2: n=196 Baseline: 48.7 ± 20.0 1 year: 46.9 ± 22.9 Relative risk [95% CI]: NR Baseline: −2.9 1 year: −6.5, 0.6	Funding: Funding was provided by Actelion Pharmaceuticals Ltd (Allschwil, Switzerland). Colleagues from Actelion Pharmaceuticals Ltd participated in the study design, the collection, analysis, and the interpretation of data. Funding for medical writing

Study details	Patients	Methods	Outcome measures	Effect size	Comments
13 countries in Europe Study design: prospective, multicentre, randomised, double-blind, placebo-controlled, parallel-group, event-driven, morbidity–mortality trial Who was blinded: (if RCT) Setting: teaching and community hospitals Duration of follow-up: 1 year	statement, of less than 3 years' duration, and with diagnosis confirmed by surgical lung biopsy Exclusion criteria: Severe concomitant illness limiting life expectancy (<1 year); severe restrictive lung disease (forced vital capacity [FVC] <50% of predicted or <1.2 L [formula reported in E1], diffusing capacity for carbon monoxide [DLCO] <30% of predicted or residual volume [RV] ≥120% of obstructive lung disease (forced expiratory volume in 1 second [FEV1] ÷ FVC <0.65); a documented, sustained improvement in IPF up to 12 months prior to randomisation; recent pulmonary or upper respiratory tract infection (≤4 weeks prior to randomisation); acute or chronic impairment (other than dyspnoea) limiting ability to comply with study requirements; chronic heart failure; serum levels of alanine aminotransferase or aspartate aminotransferase >1.5 × upper limit of normal; moderate-to-severe hepatic impairment; and, serum creatinine ≥2.5 mg·dL−1.	tolerate target dose could be maintained on initial dose Group 2 matching placebo		p value: NR	assistance during the preparation of this manuscript was provided by Actelion Pharmaceuticals Ltd Limitations: None Additional outcomes: None Notes: Eligible patients were randomized 2:1 to receive oral bosentan or matching placebo, respectively. Intention to treat analysis performed, Patients were assessed at baseline, at randomization, and every 4 months thereafter until BUILD-3 End of Study, which was scheduled to be declared when 202 primary endpoint events were confirmed. In cases of premature discontinuation of study treatment, patients underwent an End of Study Treatment assessment and
			Dyspnoea Transition dyspnoea index at 1 year	Group1: −1.7 ± 3.5 N= 383 Group 2: −1.7 ± 3.6 N= 199 Relative risk [95% CI]: 0.1 (−0.5, 0.7) p value: NR	
			Mortality	Group1: 11/407 Group 2: 6/209 Relative risk [95% CI]: NR p value: NR	
			Adverse events (observed in ≥5% of bosentan treated patients): abnormal LFTs	Group1: 30/406 (7.4%) Group 2: 0/209 (0%) Relative risk [95% CI]: NR p value: NR	
			Adverse events (observed in ≥5% of bosentan treated patients): drug hypersensitivity	Group1: 1/406 (7.4%) Group 2: 0/209 (0%) Relative risk [95% CI]: NR p value: NR	
			Time to IPF worsening (excluding death).	HR (95% CI): 0.85 (0.654-1.107)	
			Time to death up to BUILD-3 End of Study.	HR (95% CI): 1.039 (0.6-1.798)	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	Also patients were not enrolled if, within 4 weeks preceding randomization, they received chronic treatment for IPF with: oral corticosteroids (>20 mg per day prednisone or equivalent), immunosuppressive or cytotoxic drugs, antifibrotic drugs, or N-acetylcysteine. Patients treated using glibenclamide (glyburide) and calcineurin inhibitors within 1 week preceding randomization were also not enrolled All patients N: 616 Age (mean): Drop outs: 95 M/F: 429(69.6%)/187 (30.4%) Group 1 N: 407 Age (mean): 63.8 ± 8.4 Drop outs: 75 M/F: 296 (72.7%) /111(27.3%) Predicted FVC (mean ±SD): 74.9 ±14.8 Predicted DLCO (mean ±SD): 47.7 ±11.9				remained in the trial until the BUILD-3 End of Study was declared. Patients were assigned a unique randomization number via a centralized Interactive Randomization System which designated which study treatment was to be dispensed at randomization, at each patient visit to the site, and each time a patient's dose was adjusted. The randomization code was generated using Visual Basic 6.0. The investigators, study staff, patients, monitors, and study sponsor remained blinded to treatment assignment until study database closure

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	Group 2 N: 209 Age (mean): 63.2 ± 9.1 Drop outs: 21 M/F: 133 (63.6%)/76 (36.4%) Predicted FVC (mean ±SD): 73.1 ± 15.3 Predicted DLCO (mean ±SD): 47.9 ± 12.7				

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

F.6.5 N-acetylcysteine vs. Placebo

Table 87: Tomioka 2005[476]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Tomioka 2005[476] Country of study: Japan Study design:	Patient group: 26 patients: clinical diagnosis (ATS criteria); 4 patients: diagnosis based on presence of UIP by a surgical (open or thoracoscopic) lung biopsy Inclusion criteria: Patients with IPF who had not received any form of immunosuppressive therapy. Exclusion criteria: Aged 80 years or over A grave complication that would	Group 1 N-acetyl-cysteine (NAC) twice daily via a compressor-type nebuliser (OMRON NE c-16, OMRON, Tokyo, Japan). At each treatment session, patients inhaled 176mg NAC diluted with saline to a total volume of 5mL (a total of 352mg NAC	Lung capacity (% of predicted) absolute value (mean±SEM) CHESTAC-33 system (Chest, Tokyo, Japan) used. Predicted normal values for the Japanese population were derived from reference values of the Japanese Respiratory Society.	Group1: Baseline: 67.6±15.7 Change: -7.2±4.6 (SD 14.55*) Group 2: Baseline:76.6±19.1 Change: -9.6±4.2 (SD 14.55*) p value: Not sig	* Calculated by NCGC Funding: not reported Limitations: Randomisation method unclear Allocation concealment unclear Small sample size ?appropriate NAC dose
			Carbon monoxide diffusing capacity (% of predicted) (mean±SEM)	Group1: Baseline: 64.7±15.7	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
open-label RCT Who was blinded: (if RCT) open-label Setting: Outpatient pulmonary clinic Duration of follow-up: 12 months	influence the clinical course of IPF Enrolment in a rehabilitation programme Non-compliance in taking medications All patients N: 30 randomised; 22 evaluable Age (range): 57-78 years Drop outs: 8 (4 deaths, 2 lost to follow-up, 1 developed lung cancer, 1 developed thrombocytopenic purpura) Group 1 N: 15 randomised; 10 evaluable Age (mean): 70±4.9 (evaluable group) Drop outs: 5 (2 deaths due to respiratory failure, 1 lost to follow-up, , 1 developed lung cancer, 1 developed thrombocytopenic purpura) Smoking status: 5 (never), 4 (former: smoked in the past but not within previous year), 1 (current: smoked regularly within previous year) Lowest Sa02 during 6-min walking test (%): 90.1±5.9 Group 2 N: 15 randomised; 12 evaluable Age (mean): 70±5.3 (evaluable group) Drop outs: 3 (2 deaths due to respiratory failure, 1 lost to follow-up) Smoking status: 3 (never), 5 (former: smoked in the past but not within	per day) Group 2 Bromhexine hydrochloride twice daily via a compressor-type nebuliser (OMRON NE c-16, OMRON, Tokyo, Japan). At each treatment session, patients inhaled 2mg of bromhexine hydrochloride diluted with saline to a total volume of 5mL (a total of 4mg NAC per day)	CHESTAC-33 system (Chest, Tokyo, Japan) used. Predicted normal values for the Japanese population were derived from Nishida et al (1976).	Change: -10.7±6.7 (SD 21.19*) Group 2: Baseline: 60.7±16.7 Change: -9.6±6.2 (SD 21.48*) p value: Not sig	for IPF (study states it may be too low) Open label study Additional outcomes: SF-36 (Japanese test version)- overall score not provided HRCT findings Serum KL-6-values Notes: At the endpoint, corticosteroid therapy (doses of 10, 35 and 25mg/day) had been started in 3 patients (1 in NAC grp; 2 in control due to disease progression) 3 patients (1 in NAC grp; 2 in control) developed a need for supplemental oxygen during the study, but all 3 underwent the 6MWT without supplemental oxygen at endpoint.
			6 min walking test distance (m) Absolute value (mean±SEM). Performed according to the method of Chang et al (18) in an enclosed, level, measured corridor. Supplemental oxygen was permitted at the same concentration inspired normally during daily activities at baseline.	Group1: Baseline: 385±90 Change: 14.0±40.2 (SD 127.12*) Group 2: Baseline: 390±116 Change: -52.4±34.9 (SD 120.90*) p value: Not sig	
			Adverse effects	Group1: none Group 2: NR p value: Not sig	
			Lowest SaO2 during 6MWT (%)	Group 1: -0.3 ±2.1% Group 2: -6.8 ±1.8% P: <0.05	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	previous year), 4 (current: smoked regularly within previous year) Lowest Sa02 during 6-min walking test (%): 91.1±5.9				

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood , DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

F.6.6 N-acetylcysteine vs. no treatment

Table 88: Homma 2012[189]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Homma 2012[189] Comparison: NAC therapy versus nil NAC therapy Setting: Multicentre trial; 27 centres in Japan Duration of follow-up: 48 weeks Design: Parallel group	Patient group: Early stage (I or II) IPF patients aged between 50-79 years as diagnosed by ATS/ERS consensus. HRCT evidence of UIP mandatory. Inclusion criteria: Firm clinical and radiological diagnosis of IPF at stage I or II and a lowest arterial O2 saturation of > 90% during 6MWD test.	Group 1: (n=44) 352.4mg N-Acetylcysteine (NAC) diluted with saline to a volume of 4ml nebulised twice daily with microair nebulisers (NE-U222, Omron, Tokyo, Japan) Group 2: (n=46) 'No treatment (or placebo)'	Number of patients who subjectively felt their dyspnoea had improved compared to deteriorated at 48 weeks	Group 1: 33/38 Group2:32/38 NS Difference	Funding: Grant from Ministry of Health, Labour and Welfare of Japan. Authors thank Pharma KK and Niphix KK for their help with study management and data analysis Limitations: Very High Risk of Bias overall High risk selection bias:
			Mean change in FVC (l) from baseline (mean +/- SD) at 48 weeks	Group 1: -0.09 +/- 0.3 Group2: -0.15 +/- 0.2 NS Difference	
			Change in lowest SaO2 (%) during 6MWT, 6MWD (m), VC (%) and (% of predicted, DLCO (%) and (% of predicted), TLC (%) and (%) of predicted at 48 weeks	No data presented but narrative text says NS difference between group 1 and 2.	
			Number of patients with IPF exacerbation	Group 1: 1 Group 2: 4	

	Exclusion criteria: Improvement in symptoms in the preceding 3 months; use of NAC, immunosuppressive agents, oral prednisolone or pirfenidone and clinical suspicion of other interstitial pneumonia other than IPF All patients N:90 Age (mean):NR Drop outs: NR Of those analysed: Group 1: N: 38 Age (mean): 67.6 +/- 6.4 Male/female (%): 76/24 FVC, % predicted (mean +/- SD): 89.2 +/- 17.8 DLCO % predicted (mean +/- SD): 72.3 +/- 25.3 Drop outs: NR accurately Group 2: N: 38 Age (mean): 68.2 +/- 7.7 Male/female (%): 76/24 FVC, % predicted (mean			NS Difference	Randomisation process and allocation concealment not described Not commented upon any differences between baseline groups, although p values presented all non-significant Not placebo controlled, comparison 'no treatment' Blinding methods and personnel not described Only patients aged 50-79 included Selective reporting of data, LOCF method used for analysis, 10 patients data not analysed due to 'protocol violations, missing data etc' Paper suggested NS
			AEs	'NS differences in adverse events reported for two groups'. Common AEs reported during the study were bacterial pneumonia, cough, sore throat and hypercholesterolemia. Treatment with NAC was well tolerated.	
			1 and 3 year survival rate	NR	
			Hospitalisations due to IPF	NR	
			QoL	NR	
			Mortality	NR	

	+/- SD): 88.7 +/-15.5 DLCO % predicted (mean +/- SD):64.4 +/-20.1 Drop outs: NR accurately See limitations section for discussion of dropouts and selective reporting				difference in excluded from analysis population between arms. Reason for Dropouts not given and selective analysed subset. Serum markers of pneumocyte injury (KL-6, surfactant proteins A and D) Disease progression as determined by HRCT

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood , DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

F.6.7 Co-trimoxazole vs. Placebo

Table 89: Shulgina 2013[441]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Shulgina 2013 [441] Country of study:	Patient group: Fibrotic idiopathic interstitial pneumonia (89% with definite/probable IPF) Inclusion criteria: Age : >40 years MRC dyspnoea score ≥2	Group 1: co-trimoxazole 960mg twice daily orally in addition to usual care Group 2: Placebo tablets, twice daily	Mortality (ITT analysis)	Group1: 18/95 (19%) Group 2: 19/86 (22%) p value: 0.379	Funding: East Anglia Thoracic Society NIHR Research for Patient benefit programme Boehringer Ingelheim
			Mortality (per-protocol analysis)	Group1: 3/53 Group 2: 14/65	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
UK Study design: RCT Who was blinded: (if RCT) double-blind Setting: 28 university and district hospital in England and Wales Duration of follow-up:	Treatment regimens had remained unchanged for at least 6 weeks A protocol amendment was made to include patients not receiving immunosuppressive therapy as long as they had progressive disease with deteriorating lung function and those receiving anti-oxidants to reflect changes in UK prescribing practice. Exclusion criteria: Child-bearing potential Secondary cause for pulmonary fibrosis identified Receiving immunosuppressant medication other than prednisolone, azathioprine or mycophenolate mofetil Co-trimoxazole allergy or intolerance Untreated folate or B12 deficiency Respiratory tract infection within 2 months prior to randomisation Significant concomitant disease that could affect subject safety or influence study outcome. All patients N: 181 (ITT analysis) Age: 71.6 ±8.5 years (mean) FVc (% predicted): 70.7 ±21.2			p value: 0.02	non-commercial educational grant Limitations: Not all patients had IPF Patients in the co-trimoxazole group may have had shorter disease duration Additional outcomes: Hospital days Medicine increase/ decrease Oxygen increase/ decrease Notes: Outcomes presented as 'adjusted for baseline' ITT and per-protocol analysis both used Randomisation: performed centrally using a computer generated randomisation code and the site research pharmacist was
			FVC (ml) ITT analysis	Group1: -195.67 (SD 288.82) Group 2:-182.22 (SD 330.15) p value: 0.988 (95% CI -0.11, 0.11)	
			FVC % predicted ITT analysis	Group1: -4.65 (SD 9.96) Group 2: -4.79 (SD 8.7) p value: 0.978 (95% CI -3.22, 3.32)	
			DLCO (mmol/min/KPa) ITT analysis	Group 1: -0.3 (SD0.68) Group 2: -0.22 (SD 0.81) P value: 0.48 (95% CI -0.4, 0.19)	
			DLCO % predicted ITT analysis	Group 1: -3.67 Group 2: -3.88 P value: 0.459 (85% CI -4.88, 2.21)	
			SGRQ total (units)	Group 1: 0.71 Group 2: 1.78 P value: 0.599 (95% CI -6.13, 3.54)	
			6MWD (metres)	Group 1: -18.7 Group 2: -19.48	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	DLCO (% predicted): 37.5±11.5 Drop outs: Group 1 (co-trimoxazole) N: 95 Age (mean): 72.38 (SD 8.45) Definite IPF (UIP histopathology, honeycombing on HRCT or in report on destroyed HRCT): 37 Probable IPF (Fell probability score ≥0.6): 46 Probable IPF (all features consistent with UIP except honeycombing on HRCT or in report on destroyed HRCT): 46 Co-existing emphysema: 6 (6.3%) Drop outs: 4% did not receive more than 80% of the scheduled study drug doses Group 2 (placebo) N: 86 Age (mean): 70.65 (SD 8.56) Definite IPF (UIP histopathology, honeycombing on HRCT or in report on			P value: 0.835 (95% CI -53.55, 43.24)	informed of the code by email via Norwich Clinical Trials Unit. Patients were randomised with stratification for the site and the use of azathioprine/ mycophenolate mofetil. A blinded retrospective radiological review was undertaken by 2 specialist respiratory radiologists using the criteria of Silva et al., 2008 for those patients where a histopathological diagnosis of UIP or NSIP was not available. In addition, HRCT scans of patients without definite IPF were scored according to the algorithm
			6MW desaturation of 4% or more	Group 1: 16/20 (80%) Group 2: 31/35 (88.6%) P value: 0.634 (95% CI -2.37, 4.1)	
			MRC score	Group 1: 0.07 (SD 0.72) Group 2: 0.21 (SD 0.82) P value: 0.533 (95% CI -0.37, 0.19)	
			Adverse events (GI), number of individuals with 1 or more	Group 1: 41 (44.6%) Group 2: 21 (24.4%) P value: 0.005	
			Adverse events (nausea), number of individuals with 1 or more	Group 1: 17 (18.5%) Group 2: 6 (7%) P value: 0.022	
			Adverse events (immune system disorder), number of individuals with 1 or more	Group 1: 0 Group 2: 1 (1.2%) p value: 0.483	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	destroyed HRCT): 38 Probable IPF (Fell probability score ≥0.6): 41 Probable IPF (all features consistent with UIP except honeycombing on HRCT or in report on destroyed HRCT): 40 Co-existing emphysema: 9 (10.5%) Drop outs: 10% did not receive more than 80% of the scheduled study drug doses		Adverse events (skin disorder), number of individuals with 1 or more	Group 1: 14 (15.2%) Group 2: 4 (4.7%) p value: 0.019	described by Fell et al., 2010 to predict the probability of IPF.

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood , DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

F.6.8 Ambrisentan vs. Placebo

Table 90: Raghu 2012[395]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Raghu 2012 [395] Country of study: unclear (136 clinical sites)	Patient group: IPF Inclusion criteria: NR Exclusion criteria: NR All patients N: 492 Age : NR Drop outs: NR Group 1 (Ambrisentan)	Group 1 Ambrisentan Group 2 Placebo	Time to IPF disease progression, defined as all-cause mortality, adjudicated respiratory hospitalisation or a categorical decrease in lung function (a 10% decrease in FVC with a 5% decrease in DLCO or a 15% decrease in DLCO with a 5% decrease in FVC)	Group1: HR 1.74 fold increase in risk of meeting this (95% CI 1.14-2.66, p=0.01) Group 2: NR p value: Not significant	Funding: NR Limitations: limited data available- abstract only Additional outcomes: Primary events (not defined in abstract therefore NR in this
			Mortality	Group1: HR 2.05 (95% CI 0.75-5.76, p=0.1)	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Study design: RCT Who was blinded: (if RCT) double-blind Setting: 136 clinical sites Duration of follow-up: 34 weeks	N: NR Age (mean): NR Drop outs: NR Group 2 (Placebo) N: NR Age (mean): NR Drop outs: NR			Group 2: NR p value: Not significant	table) Respiratory hospitalisations Notes: Abstract only 11% of patients in each group had pulmonary hypertension
			Categorical decrease in lung function (a 10% decrease in FVC with a 5% decrease in DLCO or a 15% decrease in DLCO with a 5% decrease in FVC)	Group1: HR 1.53 (95% CI 0.84- 2.78, p=0.109) Group 2: NR p value: Not significant	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

F.6.9 Combination: Prednisolone & azathioprine vs. Prednisolone & placebo

Table 91: Raghu 1991[400]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Raghu 1991[400] Country of study: USA Study design: RCT Who was blinded: (if RCT) Patients and clinicians Setting: Outpatient Duration of follow-up: 12 months	Patient group: Newly diagnosed patients with IPF Symptomatic adult patients with diffuse pulmonary infiltrates Diagnosis: Supported by lung biopsy in all patients (23 OLB, 4 transbronchial). All fulfilled: Progressive dyspnoea from day of onset Progressive roentgenographic parenchymal abnormality 10% or greater decrease in FVC or total lung capacity compared with previous values; or 20% or greater reduction in DLCO compared with previous values Inclusion criteria: Exclusion criteria: NR All patients N: 27 M:F: 12:15 Drop outs: 8	Group 1 Azathioprine plus prednisolone. Azathioprine was administered at a daily dose of 3mg/kg/day (not to exceed 200mg/day) to the nearest 25mg dose increment for the duration of the trial. Group 2 Prednisone plus placebo. Oral prednisone dose: in an initial dose of 1.5mg/kg/day to a maximum of 100mg/day for the first 2 weeks followed by a fortnightly decrease of according to participants' tolerance until a maintenance dose of 20mg/day or less was reached. A similar number of placebo tablets were dispensed. All patients	Change in lung capacity (FVC) (% predicted) after 1 year of therapy (mean± SE) measured using an Ohio spirometer and interpreted according to Schoenberg 1978	Group1: +6.5 ±5.3 (*SD 19.83) Group 2: +1.7 ±7.4 (*SD 26.68) Mean difference: 6.4 * p value: 0.87	*Calculated by NCGC Funding: Virginia Mason Research Centre, Seattle, WA Limitations: Unclear allocation concealment Patients were allowed to cross over between groups ATS diagnostic criteria not used (HRCT not mandatory) Additional outcomes: Change in rest P[A-a]O2 (mmHg) Numbers who had improved/unchanged or deteriorated
			Change in gas transfer (DLCOSB) (% predicted) (mean± SE) after 1 year of therapy measured with a Medscience Model 572 Diffusion corrected for haemoglobin concentration and interpreted according to Ogilvie 1957 and Dinkara 1970	Group1: +7.3 ±5.3 (*SD 19.83) Group 2: +0.9 ±5.7 (*SD 20.55) Relative risk [95% CI]:NR p value: 0.70	
			Overall survival at 1 year, probability (mean± SE) (estimated from graph therefore only reported here)	Group 1: 0.72 Group 2: 0.70	
			Overall survival at 3 years, probability	Group1: 0.6 Group 2: 0.55	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	Group 1 N: 14 (randomised), 10 (evaluable) Age (mean): 58±2 M:F: 5:9 Clinical duration of illness (months):26±6 Drop outs: 4 deaths (3 resp. failure; 1 MI); 2 crossed over to other group (not counted as drop outs due to ITT analysis) Group 2 N: 13 (randomised), 9 (evaluable) Age (mean): 54±3 M:F: 7:6 Clinical duration of illness (months):23±6 Drop outs: 4 deaths (3 resp. failure; 1 MI); 1 crossed over to other group (not counted as drop out due to ITT analysis)	Received oral prednisone according to an identical protocol. The initial dose was 1.5mg/kg/day (not to exceed 100mg/day) for the first 2 weeks followed by a fortnightly decrease of 20mg/day until a dose of 40mg/day was reached. The dosage was further decreased in 5 to 10mg/day decrements every 2 weeks according to patient tolerance in an effort to achieve a maintenance dose of 20mg/day or less.	(mean± SE) (estimated from graph therefore only reported here)	Relative risk [95% CI]: p value: not significant	pulmonary function after 1 year of therapy Notes: Randomisation: block randomisation in groups of 10 by a research pharmacist Duration of patients' respiratory symptoms before lung biopsy was arbitrarily taken as the clinical duration of IPF. ITT analysis used. The patient crossed over to the other treatment arm if any of the following occurred: Nausea, vomiting or diarrhoea unresponsive to symptomatic
			Adverse events: elevated liver enzymes	Group1: 1 Group 2: 0 Relative risk [95% CI]:NR p value: (If no p-value: Sig/Not sig/NR)	
			Adverse events: infections	Group1: 4 Group 2: 1 Relative risk [95% CI]:NR p value: (If no p-value: Sig/Not sig/NR)	
			Mortality after 1 year of therapy	Group 1: 4/14 Group 2:4/13 Relative risk: 0.93 P value: NR	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
					therapy WBC<3500/ml Platelet count<80,000/ml Respiratory failure requiring mechanical ventilation Coma Abnormal LFTs Rapid disease progression Patient's request

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood , DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

F.6.10 Combination: Prednisolone & azathioprine & n-acetylcysteine vs. Azathioprine & prednisolone

Table 92: Demedts 2005[105]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Demedts 2005[105] Country of study: Multinational: 36 centres in 6	Patient group: IPF Inclusion criteria: • Age 18-75 years with a histological or radiologic pattern of UIP, with other causes ruled out	Group 1 Corticosteroids, azathioprine and acetylcysteine N-acetylcysteine (Fluimucil, Zambon Group) in 600mg	Mortality (12 month follow-up) ITT analysis	Group1: 7/80 (8.8%) Group 2: 8/75 (10.7%) Relative risk [95% CI]:0.82 (0.31-2.15) p value: 0.69	Funding: Zambon Group Limitations: High drop-out rate: only 30% of initially
			FVC (litres) (12 month follow-up) ACA	Baseline Group1: 2.29±0.68 Group 2:2.36±0.74	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
countries (Germany, France, Spain, Belgium, the Netherlands and Italy) Study design: RCT Who was blinded: patients, clinicians and investigators Setting: Duration of follow-up: 1 year	• HRCT very suggestive of, or consistent with, a diagnosis of UIP • Patients <50 years: open or thoracoscopic lung biopsy was mandatory and showed a pattern of UIP • Bronchoalveolar lavage must have been performed at any time before inclusion and must have failed to show features supporting alternative diagnoses. • Duration of disease >3 months • Bibasilar inspiratory crackles • Dyspnoea scores of at least 2 on a scale of 0 (min) and 20 (max) • Vital capacity no more than 80% predicted • Single breath DLCO <80% predicted • At least 2 of the 3 members of each committee or at least 2 members of the radiology committee (if no biopsy was available) had to confirm the diagnosis of UIP. Exclusion criteria:	effervescent tablets 3 times daily. Group 2 Corticosteroids and azathioprine Matched placebo All patients Usual care, as recommended by ATS/ERS plus: Prednisone: starting dose 0.5 per kg of body weight per day month 2: 0.4mg/kg/day month 3: 0.3 mg/kg/day dose progressively reduced to 10mg per day in months 4,5 and 6 and this dose was maintained until month 12. Azathioprine: 2mg/kg/day		12 months Group1: 2.31±0.79 n=55 Group 2: 2.26±0.72 n=51	randomised patients available for follow-up after 1 year Patients excluded after randomisation Total dose of N-acetylcysteine was 1800mg/day which is 3-9x the usual approved dose when administered in COPD Results for some outcomes not reported fully Additional outcomes: FVC (% predicted value) DLCO (% predicted value) DLCO:VA Maximum exercise load Maximum oxygen uptake Maximum
			FVC (litres) (12 month follow-up) ITT	Baseline Group1: 2.29±0.68 Group 2:2.36±0.74 12 months Group1: 2.22±0.77 n=71 Group 2: 2.17±0.71 n=68	
			DLCO (mmol/min/kPa) (12 month follow-up) ACA	Baseline Group1: 3.85±1.41 Group 2: 3.90±1.39 12 months Group1: 4.20± 2.07 n=55 Group 2: 3.46± 1.22 n=51	
			DLCO (mmol/min/kPa) (12 month follow-up) ITT	Baseline Group1: 3.85±1.41 Group 2: 3.90±1.39 12 months Group1: 3.74± 1.99 n=68 Group 2: 3.20± 1.26 n=63	
			Adverse events: abnormal LFTs ITT analysis	Group1: 14/80 (18%) Group 2: 11/75 (15%)	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	Contraindication to, or no justification for standard regimen of prednisone and azathioprine Treatment with prednisone at a dose of at least 0.5mg/kg/day or with azathioprine at a dose of at least 2 mg/kg/day during the month before inclusion in the study, or treatment with acetylcysteine at a dose of >600mg/day for >3 months in the previous 3 years. Concomitant/ pre-existing diseases, abnormalities or treatment at study entry or in the past with drugs (such as antioxidants or anti-fibrotic drugs) that interfere with the diagnosis, severity, therapy or prognosis of IPF. All patients N: 182 (randomised) Group 1 N: 92 (randomised), 80 (confirmed and included)57/80 (71%) completed study Age (mean): 62±9 M:F (%):69:31 Drop outs: 23 (prohibited therapy:3, withdrawn by				exercise ventilation CRP score HRCT score Dyspnoea Notes: 1:1 randomisation performed centrally with computer-generated randomisation list stratified in blocks of 4 according to country and whether vital capacity was less than or more than 60% of the predicted value.

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	investigator: 3, consent withdrawn: 4, adverse events: 2, noncompliance 1, other: 3, deaths due to disease progression:3 , deaths due to respiratory tract infection: 3, deaths due to heart failure: 1) Group 2 N: 90 (randomised), 75 (confirmed and included), 51/75 (68%) completed study Age (mean): 64±9 M:F (%):75:25 Drop outs: 24 (prohibited therapy:2, withdrawn by investigator: 2, consent withdrawn: 4, adverse events: 2, noncompliance 2, ineffective treatment or worsening condition: 4, deaths due to disease progression:4 , deaths due to respiratory tract infection: 1, deaths due to cardiac arrest: 1, deaths due to MI: 1, deaths due to cancer: 1)				

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity , IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

F.6.11 Combination: Prednisolone & azathioprine & n-acetylcysteine vs. Placebo

Table 93: Panther 2012[201]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Panther 2012[201] Comparison: Prednisolone, Azathiprine and NAC versus NAC alone versus placebo Setting: Multicentre trial; 25 centres in the USA Duration of follow-up: Planned for 60 weeks. At mean 32 weeks interim analysis group 1 terminated by independent safety and monitoring board, results extrapolated up to 60 weeks Design: Parallel group	Patient group: IPF patients Inclusion criteria: IPF patients aged between 35 and 85 with mild to moderate lung function impairment (FVC ≥ 50%) and DCLO ≥ 30% of predicted) meeting ATS/ERS, JRS and LATA criteria with a HRCT or biopsy 48 month or less before enrolment. Exclusion criteria: Nil quoted in paper referred to study protocol All patients N: 155 Age (mean): 68 years Male/Female (%): 75/25 Predicted FVC (mean): 71% Predicted DLCO (mean): 44%	Group 1: (n=77) Combination therapy: Prednisolone initiated at 0.5mg/kg of ideal body weight taped to 0.15mg/kg over 25 weeks, Azathioprine (max 150mg /day) dosed by patients ideal weight, concurrent use of allopurinol and TPMT activity, NAC 600mg orally tds Group 2: (n=78) Placebo Group 3: 600mg NAC orally tds (this arm of the study remains ongoing and data not presented)	All-cause mortality at trial stop	Group 1: 8 Group 2: 1 RR [95%CI]: 8.10 [1.04, 63.26] p=0.05	Funding: Zambon pharmaceuticals supplied NAC and matching placebo Limitations: Manuscript approved by Zambon pharmaceuticals prior to submission Risk of Bias: Serious: High risk attrition bias: No overall dropout rates given prior to discontinuation of combination therapy arm at 32 week interim analysis. Discontinuation rates given for individual drugs may be for same patient no time course given
			Respiratory cause mortality at trial stop	Group 1: 7 Group2: 1 Non-significant difference	
			All cause hospitalisations at trial stop	Group 1: 23 Group 2: 7 RR [95%CI]: 3.33 [1.52, 7.30] p=0.003	
			Hospitalisations due to IPF exacerbation at trial stop	Group 1: 5 Group 2: 0 Non-significant difference	
			Number of patients who discontinued all three drugs at trial stop	Group 1: 20 Group 2: 3 RR [95%CI]: 6.75 [2.09, 21.80] p=0.001	
			Change in FVC (l) from baseline (mean +/- SD) at trial stop SD calculated by NCGC	Group 1: -0.24 +/- 0.33 Group2: - 0.23 +/- 0.33 Non-significant difference	

	Group 1: N: 77 Age (mean): 68.8+/- 7.3 Male/female (n):59 /18 Predicted FVC (mean (%)): 69.3 +/- 15.1 Predicted DLCO (mean (%)): 42.1+/-10.2 Group 2: N: 78 Age (mean): 67.9 +/- 8.1 Male/female (n):57/21 Predicted FVC (mean (%)): 72.1+/-14.4 Predicted DLCO (mean(%)): 45.3 +/- 12.4 Group 3: This arm remains ongoing baseline characteristics not published Study quotes groups were 'well matched' with respect to demographic and clinical characteristics		Toxicity: Total number of patients reporting any SAE at trial stop	Group 1: 24 Group 2: 8 RR [95%CI]: 3.04 [1.46, 6.34] p=0.003	or actual number of dropouts related to toxicity at 32 weeks. ITT population studied No description of blinding methods or personnel given, Additional outcomes: All outcomes reported due to high impact nature of paper Notes: Data from group 3 of the study not presented as this arm of the study remains on-going
			Toxicity: Total number of patients reporting respiratory SAEs at trial stop	Group 1: 12 Group 2: 4 RR [95%CI]: 3.04 [1.02, 9.01] p=0.05	
			Toxicity: Total number of patients reporting GI SAEs at trial stop	Group 1: 1 Group 2: 3 Non-significant difference	
			Toxicity: Total number of patients reporting infectious SAEs at trial stop	Group 1: 5 Group 2: 1 Non-significant difference	
			Toxicity: Total number of patients reporting cardiac SAEs at trial stop	Group 1: 3 Group 2: 0 Non-significant difference	
			Toxicity: Total number of patients reporting neoplastic SAEs at trial stop	Group 1: 2 Group 2: 0 Non-significant difference	
			Toxicity: Total number of patients reporting musculoskeletal SAEs at trial stop	Group 1: 0 Group 2: 1 Non-significant difference	
			Toxicity: Total number of patients reporting metabolic SAEs at trial	Group 1: 1 Group 2: 0 Non-significant difference	

	See limitations for notes on dropout and attrition bias		stop		
			Toxicity: Total number of patients reporting nervous system SAEs at trial stop	Group 1: 1 Group 2: 0 Non-significant difference	
			Toxicity: Total number of patients reporting reproductive system SAEs at trial stop	Group 1: 1 Group 2: 0 Non-significant difference	
			Toxicity: Total number of patients reporting any AEs at trial stop	Group 1: 68 Group 2: 61 Non-significant difference	
			Toxicity: Total number of patients reporting skin AEs at trial stop	Group 1: 13 Group 2: 4 RR [95%CI]: 3.29 [1.12, 9.65] p=0.03	
			Toxicity: Total number of patients reporting renal/urinary AEs at trial stop	Group 1: 10 Group 2: 1 RR [95%CI]: 10.13 [1.33, 77.24] p=0.03	
			All-cause mortality at 60 weeks (extrapolated)	HR: 9.26 SE:	
			All-cause mortality or hospitalisation at 60 weeks (extrapolated)	HR:3.74 SE:	
			All-cause mortality or ≥10% decline in FVC at 60 weeks (extrapolated)	HR:1.46 SE:	
			1 and 3 year survival rates	NR	

			Dyspnoea	NR	
			Gas transfer	NR	
			QoL	NR	
			Performance on sub-maximal walk test	NR	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood , DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, UIP= usual interstitial pneumonia, VA= alveolar volume, CRP score= clinical, radiologic, physiological score, ACA= available case analysis

F.7 Lung transplantation

Table 94: Charman 2002[62]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Charman2002[62] Country of study: UK Study design: Retrospective cohort Who was blinded: NR	Patient group: Patients accepted for single, double and heart lung transplant between April 1984-september 1999 Inclusion criteria: Patients were required to have a life expectancy of 12-24 months, or severely impaired quality of life despite maximal medical therapy. Acceptance criteria for LTX in line with ATS, ERS and ISHLT Exclusion criteria:	All patients Patient data was routinely collected from the time they were accepted for LTX. Cohort collected from April 1984 – September 1999* Data is analysed separately for the following groups: ALL Patients n=100 Single LTX patients n=63 Double/Heart Lung Transplant patients n=37	Died on Waiting List (n)	All Patients: 33 Single LTX patients: 18 Double/Heart Lung Transplant patients: 15	Funding: NR Limitations: Doesn't specify IPF: Cohort is all Pulmonary Fibrosis Doesn't account for any confounders – no data given on disease severity at baseline. Presented as crude data Additional outcomes: The same outcomes reported for other diseases Equity point Risk profiles
			Removed or still waiting (n)	All Patients: 7 Single LTX patients: 3 Double/Heart Lung Transplant patients: 4	
			Transplanted (n)	All Patients: 60 Single LTX patients: 42 Double/Heart Lung Transplant patients: 18	
			Days Waiting (Median (IQR))	All Patients: 117 (43, 231) Single LTX patients: 104 (5,194)	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Setting: Hospital Duration of follow-up: 15 years	NR All patients N: 100 (only pulmonary fibrosis patient data reported) Age (mean±SD):49±12 Single LTX PF patients: 52±11 Double/Heart Lung Transplant PF patients: 41±11 Drop outs: 0			Double/Heart Lung Transplant patients: 147 (94,305)	Notes: *Patients listed for a second transplant were not considered twice but recorded as deaths or censored.
			Post-transplant survival days (median (95% CI))	All Patients: 931 (98,1764) Single LTX patients: 449 (0,1287) Double/Heart Lung Transplant patients: 1121 (0, 3024)	
			Risk of death after transplant relative to that of continued waiting at 1 month (RR)	All Patients: 2.23 Single LTX patients:1.96 Double/Heart Lung Transplant patients: 2.88	
			Risk of death after transplant relative to that of continued waiting at 6 months (RR)	All Patients: 0.65 Single LTX patients: 0.71 Double/Heart Lung Transplant patients: 0.57	
			Risk of death after transplant relative to that of continued waiting at 12 months (RR)	ALL Patients: 0.46 Single LTX patients: 0.54 Double/Heart Lung Transplant patients: 0.36	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St. George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 95: Chen 2009[63]

Study	Patients	Methods	Outcome	Effect size	Comments

details			measures		
Chen2009[63] Country of study: USA Study design: Retrospective cohort Who was blinded: NR Setting: Hospital Duration of follow-up: 12 months	Patient group: All lung transplantation registrants in the United States listed from May 4, 2002 to May 3, 2008 – IPF patient data is presented only Inclusion criteria: Age 18 or older with one of four primary diagnoses defined in the OPTN database: Primary Pulmonary Hypertension Idiopathic Pulmonary Fibrosis COPD/Emphysema Cystic Fibrosis. Exclusion criteria: patients classified as secondary pulmonary hypertension Listings for combined heart-lung All patients N: 2981 Drop outs: 0 Group 1	National data from United Network for Organ Sharing used to describe waiting list and post-transplant outcomes for patients before and after implementation of the LAS. The total cohort was divided by "pre-LAS'' cohort and a ''post-LAS'' cohort based on their initial date of registration for lung transplant. Group 1 - pre LAS The pre-LAS time frame was defined as the 3-year period before implementation of the LAS (May 4, 2002 to May 3, 2005). Group 2 – post LAS The post-LAS time frame was defined as the 3-year period after implementation of the LAS (May 4, 2005 to May 3, 2008).	LTX % 6 months from initial listing for LTX (Cumulative incidence (95 % CI))	Group 1: 26(23-28) Group 2: 68 (65-70) 95% CI:NR P: <0.001	Funding: Supported in part by NHLBI grant K23 HL086585 (H.C.) and NCRR UCSF-CTSI grant UL1 RR024131 (S.C.S.), and Health Resources and Services Administration contract 231-00-0115. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the U.S. Department of Health and Human Services. Conflict of Interest Statement: H.C. served as a consultant to United Therapeutics and received $1,000 in 2007 and 2008. S.C.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.A.G. has received $205,000 in research funding from Actelion Pharmaceuticals Ltd. in 2007 and 2008. M.K.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.R.H. does not have a financial relationship with a commercial entity that has an interest in the subject of
			LTX % 12 months from initial listing for LTX (Cumulative incidence (95 % CI))	Group 1: 38(36-41) Group 2: 77(74-79) 95% CI:NR P: <0.001	
			Waiting list mortality % 6 months from initial listing for LTX (Cumulative incidence (95 % CI))	Group 1: 15(13-17) Group 2: 9(8-11) 95% CI:NR P: <0.001	
			Waiting list mortality % 12 months from initial listing for LTX (Cumulative incidence (95 % CI))	Group 1: 21(19-23) Group 2: 11(10-13) 95% CI:NR P: <0.001	
			Post LTX mortality 6 months from initial listing for LTX	Group 1: 14 (11-17) Group 2: 14 (12-16) 95% CI:NR P: 0.494	

	N: 1418 Age (mean): 55-9 M/F: 895 /523 Lung request Right: 907 Left: 974 Bilateral:683 LAS score at listing: NA Drop outs: 0 Group 2 N: 1563 Age (mean): 58-9 M/F: /506 Lung request Right:758 Left:865 Bilateral:945 LAS score at listing: 40.9 (39.0-48.3) Drop outs: 0		(Cumulative incidence (95 % CI)) Post LTX mortality 6 months from initial listing for LTX (Cumulative incidence (95 % CI))	 Group 1: 21(18-25) Group 2: 20 (17-22) 95% CI:NR P: 0.494	this manuscript. C.W.H. does not have a financial relationship with a commercial entity that has an interest in the subject Limitations: Changing in referral patterns Secular trends Factors determined at organ matching may have a large impact on who receives the LTX No indication of disease severity at baseline Additional outcomes: All listed outcomes also reported for: Primary Pulmonary Hypertension, COPD/Emphysema and Cystic Fibrosis Cumulative incidence curves and comparisons of outcomes results between diseases. Notes: In the United States, donor lung allocation is overseen by the Organ Procurement and Transplantation Network (OPTN), which is operated by the United Network for Organ Sharing (UNOS)

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St. George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 96: De Oliveira 2012[10]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
De Oliveira 2012[103] Country of study: USA Study design: Retrospective cohort Who was blinded: NR Setting: Hospital Duration of follow-up: 5 years	Patient group: LTX registrants consecutive patients with advanced ILD from Jan 93- Jan 09 Inclusion criteria: As above Exclusion criteria: NR All patients N: 79 (107 total- only IPF data presented here) Drop outs: 0 Group 1 N: 33 Age (mean): 52.5-9.9 M/F: 27/6 FVC (% predicted): 47±16 History of smoking: 17 (51%) History of diabetes: 4 (12.1%)	Group 1 pre LAS Data collected from January 1993-april 2005 Group 2 LAS Data collected from May 2005- march 2009	Hospital mortality	Group 1: 3 (9.1%) Group 2: 2 (4.3%) 95% CI:NR P: 0.64	Funding: NR Limitations: Similar baseline characteristics however higher frequency of history of diabetes, and smoking in LAS group (p=0.02) Sample size Single centre – lack of generalisability Changes in medical management Additional outcomes: Post-operative outcomes Kaplan Meier graphs Notes: Medians displayed for data which was skewed
			Survival at 1 year	Group 1: 78.8% Group 2: 85.8% 95% CI: NR P: 0.98	
			Survival at 3 years	Group 1: 63.6% Group 2: 62.8% 95% CI: NR P: 0.98	
			Survival at 5 years	Group 1: 63.6% Group 2: NR 95% CI: NR P: NR	
			Time on waiting list (days median (IQR))	Group 1: 209(113-379) Group 2: 65(14-209) 95% CI: P: <0.01	
			Length of ICU stay (days median (IQR))	Group 1: 6(4-16) Group 2: 3(2-7) 95% CI:	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	LAS score:40.3(IQR; 36.7-45.1) Drop outs: 0 Group 2 N: 46 Age (mean): 57.9±6.5 M/F: 37/9 FVC (L): 48±16 History of smoking: 35 (76.1%) History of diabetes: 16 (34.8%) LAS score: 43.5 (IQR; 38.8-48.9) Drop outs: 0			P: <0.01	
			Length of hospital stay median (IQR))	Group 1: 23(16-42) Group 2: 11(9-17) 95% CI: P: <0.01	
			Readmission <30 days (%)	Group 1: 7 (21.2%) Group 2: 11 (23.9%) 95% CI: P: 0.78	

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St. George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 97: Kadikar 1997[225]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Kadikar 1997[225] Country of study: Canada Study design: Retrospective chart	Patient group: From January 1991 to June 1995, patients who were assessed for lung transplantation by the Toronto lung transplantation program.* Inclusion criteria: NR	All patients Patient data was collected from a retrospective chart review of patients who were evaluated for the program. 6MWD test; Conducted in an	Transplanted (n)	6/26	Funding: NR Limitations: 6MWD not documented for 7/26 IPF patients and no analysis conducted for IPF alone Single centre Did not account for confounding factors
			Remained on waiting list (n)	9/26	
			Died on waiting list (n)	11/26	
			6MWD	Patients on waiting list/transplanted:364.3±122.8	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
review Who was blinded: NR Setting: Hospital Duration of follow-up: 5 years	Exclusion criteria: NR All patients N: 26 IPF patients (144 total cohort) Age (mean):52.1±6.0 Drop outs: NR	enclosed hospital corridor of 52.7m. Patients were asked to walk quickly but comfortably with encouragement along the way and rests if necessary.		N=13 Patient who died: 214.9±143.6 N=6 P=0.057	Sensitivity, specificity PPV, NPV of the 6MWT in the prediction of death – using <300m and <400 m thresholds for total cohort – not IPF alone. Additional outcomes: Lung function Cardiac function The above and reported outcomes were also given for other disease populations in the cohort. Notes: *included patients diagnosed with emphysema, alpha-1-antitrypsin deficiency, IPF, primary pulmonary hypertension, eisenmengers syndrome and cystic fibrosis.

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St. George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 98: Paik 2012[374]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Paik 2012[374]	Patient group: From May 1996 to May 2011,	All patients Patient data was	Transplanted (n (%))	23/61 (37.7%)	Funding: NR

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Country of study: Korea Study design: Retrospective chart review Who was blinded: NR Setting: 5 centres Duration of follow-up: 9 years	patients who were listed for LTX. Inclusion criteria: NR Exclusion criteria: NR All patients N: 61 IPF patients (146 total cohort) Age (mean): NR Drop outs: NR	collected from a retrospective chart review of patients who were listed for LTX at 5 institutions and listed in the Korean network for organ sharing	Remained /removed from waiting list (n (%)) Died on waiting list (n (%))	3/61(4.9%) 35 (57.4%)	Limitations: Doesn't account for any confounders – no data given on disease severity at baseline. Presented as crude data Additional outcomes: Age and sex distribution for LTX Number transplanted and mortality by blood group and gender The reported outcomes were also given for other disease populations in the cohort.

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St. George's Respiratory Questionnaire, 6MWT= 6 minute walking test

F.8 Ventilation

Table 99: Alhameed 2004[12]

Study details	Patients	Methods	Outcome measures	Effect size	Comments

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Alhameed 2004[12] Country of study: Canada Study design: Retrospective cohort Who was blinded: NR Setting: ICU Duration of follow-up: 2 months	Patient group: All patients with IPF requiring MV for unknown causes of ARF who were admitted to the medical and surgical ICU units from November 1988 to December 2000. Inclusion criteria: age 18 years and older, an established diagnosis of IPF and acute exacerbation of IPF that required ICU admission Exclusion criteria: evidence of connective tissue disorders or hypersensitivity pneumonitis; presence of infection in the first five days of ICU admission; evidence of severe left ventricular dysfunction documented as an ejection fraction of less than 30%; significant history of occupational exposure; and patients with irreversible	All patients data were collected from the medical charts All patients were treated with antibiotics and systemic corticosteroids, while eight patients received chemotherapy additionally Group 1-invasive mV Intubation and MV was administered to 21 patients for a mean duration of 11 days (range two to 27 days). Group 2-non-invasive MV The other four patients were treated with non-invasive ventilation (three patients) – two with bi-level positive airway pressure, one with proportional assist ventilation and one with high flow oxygen alone. The latter individual was included in the present study because he would have been treated with MV, but he chose not to pursue this treatment	In hospital mortality 2 month mortality	Group1: 21/21 Group 2: 3/4 p value: NR Group1: 21/21 Group 2: 4/4 p value: NR	Funding: NR Limitations: Retrospective data Generalizability 1 patient who was in the NIV group but would have been treated with IMV but declined Additional outcomes: ICU clinical status Notes: IPF was defined as a specific form of chronic fibrosing interstitial pneumonia of unknown etiology with the histological appearance of usual interstitial pneumonia (UIP) on surgical (thoroscopic or open) lung biopsy In the absence of surgical lung biopsy, IPF was diagnosed based on the presence of all of the major diagnostic criteria, as well as at least three of the four minor criteria. The major criteria included: exclusion of other known causes of interstitial lung disease such as certain

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	systemic disease, e.g. end-stage neoplasm All patients N: 25 M/F: 23/2 Age (mean): 69±11 Drop outs: 0 Group 1 N: 21 M/F:NR Age (mean): NR Drop outs: NR Group 2 N: 4 M/F: NR Age (mean): NR Drop outs: NR				drug toxicities, environmental exposures and connective tissue diseases; abnormal pulmonary function studies that included evidence of restriction (reduced vital capacity, often with an increased forced expiratory volume in 1 s/forced vital capacity ratio) and impaired gas exchange (increased alveolar to arterial oxygen gradient of the partial pressure of oxygen [PaO2] at rest or exercise or decreased diffusion capacity of the lung for carbon monoxide); bibasilar reticular abnormalities with minimal ground glass opacities on high resolution computed tomography (HRCT) scan; and transbronchial lung biopsy or bronchoalveolar lavage showing no features supporting an alternative diagnosis. The minor criteria included: age older than 50 years; insidious onset of otherwise unexplained dyspnoea on exertion; duration of illness three months or longer; and bilateral inspiratory crackles.

Study details	Patients	Methods	Outcome measures	Effect size	Comments
					Acute exacerbation of IPF was defined by the following criteria: exacerbation of dyspnoea within eight to 12 weeks; development of adult respiratory distress syndrome (ARDS) criteria (based on the American and European consensus conference absence of apparent infectious agents; and ICU admission for further diagnostic workup and management Infections were ruled out by extensive surveillance cultures (including sputum, blood and urine cultures) and/or bronchoscopy with BAL in the first five days of ICU admission. The diagnosis of pneumonia was considered if the patient met the following criteria: fever and deterioration of pulmonary status with appearance of a new pulmonary infiltrate on chest radiograph, and documented pulmonary pathogens.

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 100: Blivet 2001[43]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Blivet 2001[43] Country of study: France Study design: Retrospective cohort Who was blinded: NR Setting: University hospital Duration of follow-up: NR	Patient group: Retrospectively studied all consecutive patients referred to respiratory ICU with ARF from January 1989to June 1998 Inclusion criteria: As above Exclusion criteria: Patients with a clinical history of environmental exposure, drug induced pulmonary disease or collagen vascular disease All patients N: 15 M/F: 11/4 Age (mean): 64-10 Drop outs: 0 Current smokers: 7/15 TLC % predicted:54-17*	All patients Information was collected from patients medical charts	Patients treated with NIMV	5/15	Funding: NR Limitations: Generalizability Cross over between treatment groups Confounding factors weren't accounted for Additional outcomes: Mean time between IPF diagnosis and AR leading to ICU admission Duration of clinical symptoms Medical management including the use of cyclophosphamide, steroids, and oxygen and duration of treatment HRCT findings Conditions associated with ARF in IPF patients Clinical status of patients at ICU admission-arterial blood gas levels, simplified acute physiology score, identified cause of deterioration.
			Patients treated with MV	12/15 (10 on ICU admission and 2 after failure of NIMV)	
			Mortality	NIMV: 1 MV: 10	
			Number of patients who received both NIMV & MV	2	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	FVC % predicted:55-15* FEV1 % predicted: 61-22*				Duration of ventilation Cause of death Length of ICU stay of all patients Mortality of all patients Notes: The definition ARF is: exacerbation of dyspnoea within a few days, deterioration of hypoxemia(PaO2/fraction of inspired oxygen <250), MV requirement IPF diagnosis: based on a combination of the following; persistent bilateral dry crackles on auscultation, widespread bilateral shadowing on chest radiographs or IPF related abnormalities on HRCT, PFT results showing a restrictive ventilatory defect and decreased single breath carbon monoxide diffusing capacity and /or pathologic criteria on open lung biopsy specimen. * PFTs performed a year before ARF

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 101: Fumeaux 2001[157]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Fumeaux 2001[157] Country of study: Switzerland Study design: Retrospective observational case series Who was blinded: NR Setting: Hospital Duration of follow-up:	Patient group: Patients diagnosed with PF from December 96- to march 2001. Inclusion criteria: Patients requiring MV for ARF during their ICU stay. Exclusion criteria: NR All patients N: 14 M/F: 7/7 Age (mean): 72-8.2 Drop outs: 0 TLC 60-8 FVC 72-19 FEV 69-19	All patients Patients data was retrieved from a computerized database	Patients treated with NIMV	11/14	Funding: NR Limitations: The population includes patients who have secondary PF – 3/14 patients had secondary PF associated with sarcoidosis and rheumatoid arthritis Single centre-results may be influenced by variations in the management of patients Additional outcomes: results of biopsy, HRCT and BAL Medical management including the use of azathioprine, steroids, no pharma and oxygen - duration of treatment and last dosage Disease severity- dyspnoea ranked as mild to moderate in all Symptom of ARF Time between first symptom and admission
			Patients treated with MV	14/14	
			Number of patients who received both NIMV & MV	11/14	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
NR					Patient characteristics at hospital/ICU admission Cause of ARF Length of hospital stay before ICU admission Notes: IPF was defined according to ATS criteria and secondary PF was defined by evidence of fibrosis (dyspnoea, pulmonary crackles on auscultation, PFTs, with fibrosis on HRCT and /or pulmonary biopsy) associated with a pathology known to induce secondary fibrosis. ARF was defined as acute or rapidly progressive decline in respiratory function with exacerbation of dyspnoea and hypoxia

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 102: Mollica 2010[330]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Mollica 2010[330]	Patient group: Patients admitted for	All patients Assessment of IPF Patients with ARF	Mortality (In hospital)	Group1: 15/15 (100%) Group 2: 14/19 (74%) #	Funding: NR

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Country of study: Italy Study design: Retrospective cohort Who was blinded: NR Setting: Hospital ICU Duration of follow-up: 6 months	ARF* from January 2000 to January 2007, 34 consecutive patients at S. Camillo-Forlanini Hospital, Rome. Inclusion criteria: Patients with IPF** who underwent MV for ARF for at least 12 h Exclusion criteria: Subjects with known causes of interstitial lung disease (e.g., collagen vascular diseases, radiation/drug toxicity, neoplasm, environmental exposure, infections and post-operative observation after non-thoracic procedures) All patients N: 34 M/F:26/8 Age (mean): 60±11 Drop outs: 0	The decision to initiate NIV or to perform endotracheal intubation (ETI), in the presence of the patient's acute alteration of consciousness, depended on the clinical evaluation by the attending physician in the respiratory ward. In presence of contraindications to NIV, individuals underwent ETI and invasive MV (IMV) was performed, unless patients had previously declared a wish not to be resuscitated. Patients admitted to the ICU underwent ETI with cuffed tubes (internal diameters 7.5–8.5 mm), after intravenous administration of midazolam (2.5–5 mg) or fentanyl (1 g/kg) for sedation; all patients received propofol (1.5–2 mg/kg of measured body weight); 7 patients also received vecuronium (0.1 mg/kg) or pancuronium (0.05 mg/kg) to obtain a better adaptation to MV. Both IMV and NIV were performed by Puritan Bennett 7200A ventilator (Nellcor Puritan Bennett Inc. 4280, Pleasanton, Calif., USA). All along the stay, corticosteroids (methylprednisolone 0.5–1 g/day) and broad-spectrum antibiotic regimens were administered to all the patients.		p value:	Limitations: The disease severity was quite different between the 2 groups, with patients undergoing IMV showing a significantly higher APACHE II score as compared with subjects undergoing NIV (24.2 ± 6 vs. 19.5 ± 5.9; p = 0.01) Additional outcomes: reason for admission APACHE) II score duration of MV Effectiveness of MV was calculated NIV failure, ETI mortality rate (%) Notes: * ARF was defined as an acute and rapidly progressive decline in respiratory function and exacerbation of dyspnoea within a few days, associated with a deterioration of hypoxemia with a partial pressure of arterial oxygen/fraction of inspired oxygen ratio (PaO2/FiO2) < 250
			Mortality (6 month)	Group1: 15/15 Group 2: 18/19 p value:	

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	Group 1- invasive MV N: 15 M/F: NR Age (mean):64.6±10 Drop outs: 0 Group 2- non-invasive MV N: 19 M/F: NR Age (mean):56±11 Drop outs:	Group 1 IMV was applied in a volume-controlled mode with a mean delivered tidal volume (TV) value of 7.5ml/kg (range 6–9) of measured body weight. Positive end expiratory pressure (PEEP) was set in order to obtain the best oxygenation with the fewest side effects on haemodynamics Group2 NIV was performed in pressure support mode (NIPSV); a helmet (CaSta; Starmed, Mirandola, Italy) was used as an interface for all patients. Pressure support, PEEP and flow-by trigger values were adjusted in order to obtain the best oxygenation and to reduce RR and were modified on the basis of blood gas data. The criteria for NIPSV discontinuation and shift to IMV were: onset of coma, cardiovascular instability or poor compliance to NIV device.			Sepsis and shock diagnoses were based on American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (1992) criteria ** In 16 subjects, the diagnosis was obtained by lung biopsy, and in the remaining 18 by the presence of all major and at least 3 minor European Respiratory Society/American Thoracic Society criteria for IPF diagnosis All patients had severe functional and radiological impairment. On hospital admission, microbiological investigations for a suspected pulmonary infection (sputum culture and/or endotracheal aspiration and/or BAL) were performed upon all patients, before the introduction of an empirical antibiotic treatment. # despite the observed improvement in oxygenation, NIV was withdrawn because of

Study details	Patients	Methods	Outcome measures	Effect size	Comments
					poor compliance (3 patients), pneumothorax (1 patient) and blood emesis (1 patient). All of them requested not to be resuscitated and died after 16 ± 5.4 days. NIV failed to improve PaO2 /FiO2 in 9 individuals: 5 underwent IMV and died after 8.8 ± 5.8 days and 4 died before undergoing ETI.

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 103: Stern 2001[449]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Stern 2001[449] Country of study: France Study design: retrospective cohort Who was	Patient group: 27 consecutive patients with pulmonary fibrosis requiring MV for ARF admitted between September 1990 and October 1999 were retrospectively examined. Inclusion criteria: A diagnosis of IPF was based on the association of the three following criteria: (1)	All patients The decision of initiating IMV depended on the attending physician** The patients were receiving mechanical ventilation using Cesar (Taema; Paris, France), Erica (Engstro¨m; Bromma, Sweden), or Evita 2 (Dra¨ger Medical; Lübeck, Germany) ventilators. The initial settings of the ventilator were adjusted in order to minimize peak airway pressure and to maintain adequate ventilation. To accomplish the goal of limiting peak airway pressure, Paco2 was permitted to rise.	In hospital Mortality	Group1: 22/23* p value: NR	Funding: NR Limitations: Blinding No comparison/ control group Observational data Retrospective Single centre Small sample size Additional outcomes: The presence of organ

Study details	Patients	Methods	Outcome measures	Effect size	Comments
blinded: NR Setting: Hospital-ICU Duration of follow-up: NR	history of dyspnoea and examination findings compatible with the diagnosis of IPF (bilateral crackles and/or clubbing); (2) chest radiograph and/or high-resolution CT scan showing typical pattern of IPF, such as ground-glass areas, irregular linear opacities, and honeycombing; and (3) no known cause of pulmonary fibrosis, such as hypersensitivity pneumonitis connective tissue disease, drug or radiation-induced pneumonitis, or less frequent causes. Exclusion criteria: Other causes of pulmonary fibrosis All patients N: 23 M/F:19/4 Age (mean):53 Drop outs: 0	The fraction of inspired oxygen (Fio2) was 100% at the time of intubation and was then progressively decreased to the lowest level compatible with arterial oxygen haemoglobin saturation >90%. Thereafter, these settings were adjusted by the attending physician. After intubation, there were no decisions of withdrawal of support or of "do not resuscitate." At the time of intubation (day 0), volume-control ventilation was used with tidal volume ranging from 8 to 13 mL/kg and respiratory rate from 16 to 20 breaths/min. The corresponding mean peak airway pressure that resulted at day 0 was 50 6 7 cm H2O (range, 25 to 85 cm H2O).			dysfunction and/or infection in ICU was evaluated using the organ dysfunction and/or infection (ODIN) model. Duration of MV, percentage of patients who underwent LTX, Arterial blood gas measurements obtained before initiation of MV and at different time points after MV, the Pao2 value measured before MV. After MV, the Pao2/Fio2 ratio was calculated. The incidence of nosocomial pneumonia in patients receiving MV and the precipitating cause of ARF Notes: * With the exception of one patient who successfully received a single-lung transplant 6 h after initiation of MV, the remaining 22 patients died while receiving MV ** This decision was based on the presence of at least one of the two following criteria of respiratory failure: severe dyspnoea with marked deterioration of oxygen saturation, or oxygen

Study details	Patients	Methods	Outcome measures	Effect size	Comments
					saturation, 80% despite a high oxygen flow rate using a high concentration facial mask (Rusch Medical; Le Paget, France), or acute alteration of consciousness with or without marked hypercapnia. The duration of MV varied greatly among these 22 patients (median 3 days; range, 1 h to 60 days) Two patients died within the first 2 h after initiation of MV, and 10 patients (45%) died by the end of day 2. In the 10 patients who died within the first 2 days after intubation, the cause of death was oxygenation failure and severe alveolar hypoventilation associated with hemodynamic failure in 8 patients. The other causes of death were brain death related to severe hypoxemia (n = 1) and septic shock associated with left ventricular failure (n = 1).

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 104: Saydain 2002[423]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Saydain 2002[423] Country of study: USA Study design: Retrospective cohort Who was blinded: NR Setting: ICU Duration of follow-up: NR	Patient group: patients with IPF admitted to the ICU between January 1995 and July 2000 Inclusion criteria: had IPF based on the following criteria: (1) surgical biopsy showing usual interstitial pneumonitis (UIP); (2) abnormal pulmonary function studies that included evidence of restriction, and/or increased alveolar-arterial oxygen tension gradient at rest or during exercise, or decreased diffusing capacity for carbon monoxide; and (3) chest radio graph or high-resolution computed tomography suggestive of UIP. In the absence of surgical biopsy, patients had to fulfil all of the major criteria and at least three of the four minor criteria of the ATS & ERS Exclusion criteria:	This study was aimed to describe the clinical course and outcome of patients with IPF admitted to the ICU. Group 1- ventilated patients (invasive and non-invasive) Group 2- no ventilation	In hospital mortality*	Group1: 13/19 Group 2: 10/19 p value: NR	Funding: Robert N. brewer family foundation and the mayo foundation Limitations: Observational data Generalizability – single centre data Additional outcomes: Observational data recorded throughout ICU stay. Notes: Of the 32 patients admitted for respiratory failure, 10 (31%) had pneumonia, 2 (6%) pulmonary embolism, 2 (6%) congestive heart failure, and 2 (6%) pneumothorax. One patient developed acute on chronic respiratory failure following surgery for mitral valve replacement. The remaining 15 (47%) patients with respiratory

Study details	Patients	Methods	Outcome measures	Effect size	Comments
	Patients who have known causes of interstitial lung disease, such as collagen vascular disease, drug toxicity, and environmental exposure, Patients who were admitted to ICU for electrocardiographic monitoring or postoperative observation after non thoracic procedures All patients N: 38 M/F: 25/13 Age (mean): 69±11 Drop outs: 0 Group 1 N: 19 M/F: NR Age (mean): NR Drop outs: 0 Group 2 N: 19 M/F:NR Age (mean): NR Drop outs: 0				failure had no immediate precipitating factor, and the worsening respiratory failure was attributed to progression of IPF *Nineteen patients (50%) received mechanical ventilation for an average of 10.5 ± 12.4 (median 5) days. Six patients received invasive as well as non-invasive positive pressure ventilation, whereas one patient received non-invasive positive pressure ventilation only. Fifteen patients (39%) requested not to be resuscitated. Life support was withdrawn from eight patients (21%) at the request of next of kin. Ten of the 19 patients (53%) who did not receive mechanical ventilation died compared with 13 of the 19 patients (68%) who received mechanical ventilation p=0.51 There was no significant difference in the duration of mechanical ventilation between survivors and no survivors (p = 0.10). (median of 4.5 for

Study details	Patients	Methods	Outcome measures	Effect size	Comments
					survivors and of 11.0 for no survivors, p =0.66)

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

Table 105: Yokoyama 2010[504]

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Yokoyama 2010 [504] Country of study: Japan Study design: retrospective cohort Who was blinded: No one Setting: Hospital	Patient group: Patients included in the study diagnosed with IPF and were who fulfilled the proposed Japanese Respiratory Society criteria for acute exacerbation-IPF* during the period between April 1998 and June 2004 at Tosei General Hospital. Inclusion criteria: NIV was initiated in cases of a respiratory failure of PaO2/FIO2 less than 300, Exclusion criteria: Patients had contraindications of NIV use such as severe coma and pneumothorax.	All patients Standard microbiological investigations with blood and sputum cultures were performed to exclude pulmonary infection in all patients# BAL was performed on admission to rule out infectious disease except in patients with severe pulmonary function impairment before AE, marked honeycombing on HRCT, or rejection of BAL##. High-dose corticosteroid therapy was introduced as general therapy for AE-IPF. Another immunosuppressive therapy such as cyclophosphamide or cyclosporine A was concurrently or subsequently used###. Ventilatory managements BiPAP Vision (Respironics Inc, Murrysville, PA, USA) was used for NIV. The initial setting for NIV was CPAP	Mortality (all) Mortality (non-intubated cases)-NIMV Mortality (intubated cases)- MV	Group1: 6/11 p value: NR Group1: 2/7 p value: NR Group1: 4/4 p value: NR	Funding: Grant from Japanese ministry of health, labour and welfare. Limitations: No comparison/ control group Observational data Retrospective Single centre Small sample size Post hoc analysis of NIMV vs. IMV Baseline data not given per group Notes: *IPF was defined according to American Thoracic Society (ATS)/European Respiratory Society (ERS) Consensus Statement Criteria. The criteria

Study details	Patients	Methods	Outcome measures	Effect size	Comments
Duration of follow-up: 3 months	All patients N: 11** M/F:7/4 Age (mean): 72.3± 7.7 years Drop outs: 0	mode and the CPAP level was gradually increased to 12 cmH2O. Pressure support was given if high respiratory frequency or respiratory acidosis was found, and FIO2 was set at the lowest value to keep PaO2 at more than 60 mmHg. Endotracheal intubation was performed in patients with any of the following criteria: decreased alertness or major agitation requiring sedation, clinical signs of exhaustion (active contraction of the accessory muscles of respiration with paradoxical abdominal or thoracic motion), hemodynamic instability, cardiac arrest, or refractory hypoxemia. The criteria for the end of NIV use were defined as follows: PaO2/FIO2 >200, respiration rate <20, clinical improvement of the radiological findings			for AE-IPF were as follows: During the chronic course of IPF, there was 1) acute worsening of dyspnoea within the course of one month, 2) bibasilar honeycombing with newly developing ground glass attenuation and/or consolidation on HRCT scans, 3) deterioration of PaO2 of more than 10 mmHg under the same condition, and 4) exclusion of other known causes of exacerbation, such as pulmonary infection, pneumothorax, malignancy, pulmonary thromboembolism, and heart failure ** Ten patients were diagnosed with IPF before acute exacerbation and one patient was diagnosed with IPF in acute exacerbation #All blood cultures were negative, and neither sputum Gram staining nor culture was contributory. After these diagnostic investigations, broad-spectrum antibiotics were administered as empiric

Study details	Patients	Methods	Outcome measures	Effect size	Comments
					therapy until the offending pathogen was identified or ruled out. ##BAL was performed during acute exacerbation before antibiotics were introduced in 6 patients. In all 6 cases, BAL fluid studies for routine bacterial organisms, opportunistic pathogens, as well as common viral pathogens revealed no evidence of infection. ###After diagnosis of AE-IPF, all patients were treated with steroid pulse therapy and/or methyl-prednisolone 2 mg/kg/day, followed by tapering corticosteroid with or without an immunosuppressant. The time from introduction of NIV to steroid therapy was 2.2±1.2 days Duration of NIV was 5.4±3.8 days in all cases Intubation was required in 4 of 11 patients, who failed NIV.

Study details	Patients	Methods	Outcome measures	Effect size	Comments
					And the all 4 patients died during 3 months after AE-IPF. Intubation was avoided in 5 of 11 patients, who survived more than 3 months after AE-IPF. The other 2 patients, who refused endotracheal intubation, died without intubation. All 6 patients who failed NIV died within 3 months because of the progression of respiratory failure

Abbreviations: M/F=male/female, N=total number of patients randomised, SD= standard deviation, %FVC= Forced vital capacity (percentage), PaO2=partial pressure of oxygen in arterial blood, DLCO=Carbon monoxide diffusing capacity, IPF= Idiopathic Pulmonary Fibrosis, HRCT= high resolution computed tomography, HR=hazard ratio, BDI= baseline dyspnoea index, SGRQ= St.George's Respiratory Questionnaire, 6MWT= 6 minute walking test

F.9 Patient review and follow-up

No relevant clinical studies comparing different timings and delivery of review appointments were identified

Appendix G: Economic evidence tables

G.1 Diagnosis

No relevant economic evaluations were identified that assessed the value of a biopsy, multidisciplinary team consensus in the diagnosis of IPF or how this should best be achieved.

G.2 Prognosis

No health economic literature assessing an intervention for a prognostic purpose in an IPF population was identified.

G.3 Pulmonary rehabilitation

No relevant economic evaluations that assessed pulmonary rehabilitation in an IPF population were identified.

G.4 Best supportive care

No relevant economic evaluations comparing strategies of oxygen management, or palliation of cough, breathlessness or fatigue were identified.

G.5 Pharmacological interventions

G.5.1 Combination: Prednisolone & azathioprine & n-acetylcysteine vs. Conservative treatment and thiopurine S-methyltransferase testing

Table 106: Hagaman 2010[171]

J. T. Hagaman, B. W. Kinder, and M. H. Eckman. Thiopurine S-methyltranferase testing in idiopathic pulmonary fibrosis: a pharmacogenetic cost-effectiveness analysis. Lung 188 (2):125-132, 2010.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**

J. T. Hagaman, B. W. Kinder, and M. H. Eckman. Thiopurine S-methyltranferase testing in idiopathic pulmonary fibrosis: a pharmacogenetic cost-effectiveness analysis. Lung 188 (2):125-132, 2010.				
Economic analysis: CUA **Study design:** Analytic decision model **Approach to analysis:** Decision tree structure depicted however assumed Markov based on description. Based on published estimates and expert opinion **Perspective:** USA, Medicare **Time horizon:** Lifetime, with key intervention related events captured only in first year. Events assumed to occur every 0.5 years **Treatment effect duration:** Assumed to be continuous with use of drug **Discounting:** NR	**Population:** IPF patients **Cohort settings:** Start age = NR M =NR **Intervention 1:** Conservative therapy, medical history and exam. **Intervention 2:** Azathioprine, NAC, and steroids at standard dose [dose NR], medical history and exam 3 times annually, monthly CBC for 1 year and bimonthly after, LFT and renal function biannually, PFT and CT scan annually, DEXA scanning, bisphosphate therapy, calcium, and Vitamin D, TMP/sulfa 3 times weekly **Intervention 3:** Azathioprine, NAC, and steroids at reduced dose [dose NR], medical history and exam 3 times annually, monthly CBC for 1 year and bimonthly after, LFT and renal function biannually, PFT and CT scan annually, DEXA scanning, bisphosphate therapy, calcium, and Vitamin D, TMP/sulfa 3 times weekly	**Total costs (mean per patient):** Intvn 1: £6,249.78 Intvn 2: £10,190.81 Intvn 3: £10,201.12 **Currency & cost year:** 2007 US dollars (presented here as 2007 UK pounds‡) **Cost components incorporated:** TPMT assay:£193.47 Cost of delivering Intvn. 1 per month = £42.56 Cost of delivering Intvn. 2 per month = £191.54 Cost of delivering Intvn. 3 per month = £154.78 Complicated leukopenia = £6,536.77 Complicated leukopenia leading to death = £9,458.19 Uncomplicated leukopenia = £272.80 Cost of IPF progression (Interstitial lung disease DRG code 93, additional CT and PFT per year, additional comprehensive medical	**Primary outcome measure:** QALYs (mean per patient) Intvn 1: 2.50 Intvn 2: 2.61 Intvn 3: 2.62	**Primary ICER (Intvn 2 vs. Intvn 1):** Intervention 2 was subject to extended dominance ICER of Intvn3 vs. 1: £31,701.per QALY gained CI: NR Probability cost-effective: NR **Other:** If conservative treatment is excluded from the incremental analysis due to lack of applicability to the UK context, the ICER of Intvn 3 vs. 2 is £19,129.85 **Subgroup analyses: NA** **Analysis of uncertainty:** Deterministic sensitivity performed for majority of inputs except costs. A threshold analysis was conducted for prevalence of abnormal activity. Inspection from graph suggests that in order for TPMT testing to be cost effective compared to no testing, the prevalence of abnormal TPMT activity needs to be 2.5%. At prevalence above 13.5% TPMT testing dominates. The sensitivity analysis also showed that results were sensitive to the probability of leukopenia. If the probability of leukopenia on low dose of azathioprine increases above 12% over the base case value (21.4% with intermediate TPMT activity) then testing is no longer cost effective at $50,000 threshold [results not reported] A two way sensitivity analysis assessing cumulative probability of disease progression on conservative therapy and that of the drug regimen. This showed with lower estimates of disease progression on conservative therapy the less favourable the drug regimen was in comparison.

J. T. Hagaman, B. W. Kinder, and M. H. Eckman. Thiopurine S-methyltranferase testing in idiopathic pulmonary fibrosis: a pharmacogenetic cost-effectiveness analysis. Lung 188 (2):125-132, 2010.				
		exam every 6 months) = £9,527.20		Authors reported no other parameters tested influenced the results significantly.
Data sources				
Health outcomes: Respective 1 year cumulative probability of developing leucopoenia with standard dose was 1%, 21.4%, 100% for normal, intermediate and absent TPMT activity. Respective 1 year cumulative probability of developing leucopoenia with reduced dose was 1%, 10%, and NA for normal, intermediate and absent TPMT activity. 1 year probability of miscellaneous complications on azathioprine was 2.5%. In patients with leucopoenia the probability of complicated leukopenia was 16% and 8% probability of death. The one year probability of disease progression for patients on the pharmacological regimens was 37% and 51% for those without. The respective quality of life estimates used was 0.63, 0.95 and 0.76 for patients with progression of IPF, leucopoenia and complicated leucopoenia. Excess mortality due to IPF was 9% per year. Life expectancy after IPF diagnosis was 3 years. All values were subject to sensitivity analysis. Effectiveness data for the drug regimen was derived from one RCT and two observational trials - Demedts et al (2005), Raghu et al (1991), Winterbaurer et al (1978) **Quality-of-life weights:** IPF weights derived from Japanese population using SF36. Other weights derived from Eldar-Lissai et al (2008), Vogel et al (2005), Talcott (2000) **Cost sources:** Drug costs from www.drugstore.com; other costs from average Medicare reimbursement for the corresponding Current Procedural Terminology or Diagnosis Related Group codes.				
Comments				
Source of funding: Not reported; **Limitations:** Lifetime horizon used with no events associated with the intervention occurring beyond the first year, potentially not capturing some of the benefits of having appropriate dose beyond first year. Implicit assumption that if you have an adverse event due to inappropriate dosage this will occur in first year of treatment. Relevant health outcomes are included. Where possible RCT data is used, supplemented by observational data and expert opinion. Unclear if cost estimates come from the best source of data. Deterministic sensitivity performed and incremental analysis presented. No probabilistic sensitivity analysis. **Other:** Unclear whether marginal cost between conservative treatment and triple therapy applicable to UK context.				
Overall applicability*: Partially applicable **Overall quality**: Potentially serious limitations**				

Abbreviations: CBC = Complete Blood Count; CI = confidence interval; CT = Computer-aided Tomography CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; LFT = Liver Function Test; NA = Not applicable; NAC = N-acetylcysteine; NR = not reported; pa = probabilistic analysis; PFT = Pulmonary Function Test; QALY = Quality Adjusted Life Year; RCT = Randomised Control Trial; TPMT = Thiopurine S-methyltranferase; ‡ Converted using 2007 Purchasing Power Parities

** Directly applicable / partially applicable / Not applicable; ** Minor limitations /potentially serious Limitations / Very serious limitations*

G.6 Lung transplantation

No relevant economic evaluations comparing different timing of LTX in a population of IPF were identified.

G.7 Ventilation

No relevant economic evaluations comparing invasive and non-invasive ventilation strategies were identified.

G.8 Patient review and follow-up

No relevant economic evaluations comparing different review and monitoring strategies were identified.

Appendix H: Interpreting post-test probabilities by considering prevalence/pre-test probability

Predictive values or post-test probabilities address the chances of a person having a particular diagnosis given the known test result. However, the values are only accurate for a population with similar prevalence to the population tested because the prevalence of disease in the population can have a large effect on the calculated predictive value. Therefore, the predictive values are not independent of prevalence and are not intrinsic to the test itself.

Consequently, it is necessary to consider the prevalence when interpreting the positive and negative predictive values. In this report, the modified positive and negative predictive values have been calculated, which represent the value-added predictive figures:

Value-added PPV *= PPV – prevalence*

Value-added NPV *= NPV – (1 – prevalence)*

These figures convey the additional certainty of the diagnosis that is contributed by a positive or negative test result over the starting probability of a diagnosis (the prevalence in the sample). However, it is important to bear in mind that if there is only a small amount of uncertainty in the diagnosis before the test a small absolute increase in certainty may be important for diagnostic decisions.

Below is a summary matrix to aid interpretation of these values when the post-test probability is high, which superficially suggests a high diagnostic accuracy. Note that if the PPV or NPV is low then the test is unlikely to be useful as it will be unable to accurately discriminate a positive from a negative diagnosis in the majority of cases.

Table 107: Interpreting high post-test probabilities

Prevalence (pre-test probability)	Post-test probability (predictive values)	
	PPV high	NPV high
High	Little value added: limited additional certainty in the diagnosis and so uncertain in the discriminative ability of the test (accurately detected those with disease but there was a large proportion of positives in the sample)	Large value added: considerable additional certainty in the negative diagnosis and so high value of the test (accurately detected those without disease from a small total number of negatives)
Low	Large value added: considerable additional certainty in the positive diagnosis and so high value of the test (accurately detected those with disease from a small total number of positives)	Little value added: limited additional certainty in the diagnosis and so limited value of the test (accurately detected those with disease but there was a large proportion of negatives in the sample)

Appendix I: Calculations of standard errors from HR, RR and ORs

These formulae were applied for any ratio measures including HR, RR and OR

Using the Confidence Interval for the RR/OR/HR to find the SE

OR/RR/HR =	0.48
Upper CI limit =	0.69
Lower CI limit =	0.33
% CI (enter 0.95 for 95%; or 0.90 for 90%CI or 0.99 for 99%CI) =	0.95
No. of participants in Group 1 =	107
No. of participants in Group 2 =	2911

(divisor = *3.92* *)*

ln (RR)	*SE(ln RR)*
-0.7339692	**0.188163**

I.1.1 Calculations of SE

Guideline section	Study ID	Outcome & Prognostic factor	RR/OR/HR	Lower CI	Upper CI	ln(RR/OR/HR)	SE (ln RR RR/OR/HR)
Prognosis: PFTs	DuBois2012A[4]	All-cause mortality: Baseline FVC </=50% vs. >/=80%:	-	-	-	-	-
		All-cause mortality: Baseline FVC 51% - 65% vs. >/=80%:	-	-	-	-	-
		All-cause mortality: Baseline FVC 66%-79% vs. >/=80%:	-	-	-	-	-
	Caminati 2009 [53]	Mortality: Baseline resting room air arterial oxygen saturation	0.816	0.537	1.241	-0.203340924	0.21369252
		Mortality: Baseline FVC (L)	2.73972603	8.064516	0.927644	1.007857925	-0.55167887
		Mortality: Baseline DLCO (mL/min/mmHg)	1.38312586	1.824818	1.048218	0.324346057	-0.14142561
	DuBois2011A [117]	Mortality: Change in percent-predicted FVC	5.79	2.55	13.15	1.756132292	0.41845112

Guideline section	Study ID	Outcome & Prognostic factor	RR/OR/HR	Lower CI	Upper CI	ln(RR/OR/HR)	SE (ln RR RR/OR/HR)
		(from baseline) </=50% vs. >/=80%:					
Prognosis PFTs:		Mortality: Change in percent-predicted FVC (from baseline) 51% - 65% vs. >/=80%:	3.54	1.95	6.44	1.264126727	0.3047702
		Mortality: Change in percent-predicted FVC (from baseline) 66%-79% vs. >/=80%:	2.2	1.19	4.09	0.78845736	0.31494685
	DuBois2011B [121]	Mortality: Change in percent-predicted FVC (from baseline) </=50% vs. >/=80%:	7.44	3.28	16.87	2.006870849	0.41777895
		Mortality: Change in percent-predicted FVC (from baseline) 51% - 65% vs. >/=80%:	4.09	1.87	8.98	1.40854497	0.40027078
		Mortality:	1.97	0.85	4.55	0.678033543	0.42797096

Guideline section	Study ID	Outcome & Prognostic factor	RR/OR/HR	Lower CI	Upper CI	ln(RR/OR/HR)	SE (ln RR RR/OR/HR)
Prognosis: PFTs		Change in percent-predicted FVC (from baseline) 66%-79% vs. >/=80%:					
	Hallstrand 2005 [172]	Mortality: Baseline resting room air arterial oxygen saturation	1.06	0.83	1.37	0.058268908	0.12784192
	Hamada 2007 [173]	Mortality: Baseline % DLCO <40	2.7	1.46	4.99	0.993251773	0.31352027
	Jeon 2006 [219]	Mortality: Baseline FVC, % predicted per 10% decrease	1.30384048	1.095445	1.516575	0.265314126	0.08298311
		Mortality: Baseline DLCO, % predicted per 10% decrease	1.5	1.1	1.2	0.405465108	0.02219678
	Kurashima 2010 [260]	Mortality: Baseline FVC, % predicted per 1 %	0.94142282	0.845537	1.05101	-0.060362906	0.05549377
		Mortality: Baseline DLCO, % predicted per 1 %	0.87734727	0.745062	1.020181	-0.130852395	0.08017044
	Lynch 2005 [292]	Mortality: Baseline % predicted DLCO	1.85661333	2.867972	1.223881	0.618754037	-0.21723931

Guideline section	Study ID	Outcome & Prognostic factor	RR/OR/HR	Lower CI	Upper CI	ln(RR/OR/HR)	SE (ln RR RR/OR/HR)
Prognosis: PFTs	Manali 2008 [300]	Mortality: Baseline FVC, % predicted	0.97823198	1.022754	0.935765	-0.022008443	-0.02267583
	Mejia2009[311]	Mortality: Baseline FVC <50% predicted	2.6	1.19	5.68	0.955511445	0.39872396
	Mogulkoc 2001A [327]	Mortality: Baseline DLCO, % predicted per 1% decrease	1.55196035	2.111156	1.1398	0.439518875	-0.15724058
	Mura 2012[333]	Mortality: Baseline DLCO % predicted	0.93	0.89	0.97	-0.072570693	0.02195781
	DuBois2012A[4]	All-cause mortality: 24 week change in percent-predicted FVC </=10% vs. >-5%:	-	-	-	-	-
		All-cause mortality: 24 week change in percent-predicted FVC -5% - -9.9% vs. >-5%:	-	-	-	-	-
	DuBois2011A [117]	Mortality: 24 week absolute change in percent –predicted FVC </=-10% vs. >-	7.99	5.26	12.14	2.07819076	0.21336091

Guideline section	Study ID	Outcome & Prognostic factor	RR/OR/HR	Lower CI	Upper CI	ln(RR/OR/HR)	SE (ln RR RR/OR/HR)
Prognosis: PFTs		5%					
		Mortality: 24 week absolute change in percent –predicted FVC -5 to -9.9% vs. >-5%	2.6	1.75	3.85	0.955511445	0.20113708
	DuBois2011B [121]	Mortality: 24 week absolute change percentage predicted FVC </=-10% vs. >-5%:	4.78	3.12	7.33	1.564440547	0.2178935
		Mortality: 24 week absolute change percentage predicted FVC -5 to -10% vs. >-5%	2.14	1.43	2.3	0.760805829	0.12123334
	Caminati 2009 [53]	Change in oxygen saturation over 12 months follow up compared to baseline	4	13.33333	1.194743	1.386294361	-0.61539183
		Mortality: Change in FVC at 12 months	7.04225352	55.55556	0.909091	1.951928221	-1.04915656
		Mortality: Change in DLCO at 12 months	2.04081633	4.310345	0.965251	0.713349888	-0.38173088
	Mogulkoc 2001A	DLCO % predicted	2.22834787	4.364073	1.128315	0.801260445	-0.34507145

Guideline section	Study ID	Outcome & Prognostic factor	RR/OR/HR	Lower CI	Upper CI	ln(RR/OR/HR)	SE (ln RR RR/OR/HR)
	[327]	per 1% decrease, at 2 years					
	Richeldi 2012A[410]	Death at 2 years ≥5% decline in % predicted FVC at 12 months. Relative change	1.61	0.89	2.92	0.476234179	0.30309118
		Death at 2 years (time to event) ≥10% decline in % predicted FVC at 12 months. Relative change	2.75	1.46	5.17	1.011600912	0.32256027
		Death at 2 years (time to event) ≥15% decline in % predicted FVC at 12 months. Relative change	3.18	1.16	6.26	1.156881197	0.43004086
		Death at 2 years ≥5% decline in % predicted FVC at 12 months. Absolute change	2.89	1.53	5.46	1.061256502	0.32453598
		Death at 2 years (time to event) ≥10% decline in % predicted FVC at 12	2.41	1.15	5.05	0.879626748	0.37745569

Guideline section	Study ID	Outcome & Prognostic factor	RR/OR/HR	Lower CI	Upper CI	ln(RR/OR/HR)	SE (ln RR RR/OR/HR)
		months. Absolute change					
		Death at 2 years (time to event) ≥15% decline in % predicted FVC at 12 months. Absolute change	2.49	1.02	6.06	0.91228271	0.45456816
	Schmidt2011[424]	Mortality: Change in FVC over 6 months – 5% predicted	1.8	1.2	2.7	0.587786665	0.20686995
		Mortality: Change in FVC over 6 months – 10% predicted	1.4	0.9	2.1	0.336472237	0.21614741
		Mortality: Change in FVC over 6 months – 15% predicted	1.1	0.6	1.8	0.09531018	0.28025824
		Mortality: Change in FVC over 6 months – 20% predicted	2.0	1.0	4.0	0.693147181	0.35364652
		Mortality: Change in FVC over 12 months – 5% predicted	1.8	1.2	2.9	0.587786665	0.22509928

Guideline section	Study ID	Outcome & Prognostic factor	RR/OR/HR	Lower CI	Upper CI	ln(RR/OR/HR)	SE (ln RR RR/OR/HR)
		Mortality: Change in FVC over 12 months – 10% predicted	2.4	1.5	3.8	0.875468737	0.23712652
		Mortality: Change in FVC over 12 months – 15% predicted	2.6	1.6	4.5	0.955511445	0.26379433
		Mortality: Change in FVC over 12 months – 20% predicted	3.6	1.9	6.9	1.280933845	0.32899682
		Mortality: Change in DLCO over 6 months – 10% predicted:	1.7	1.1	2.5	0.530628251	0.20943381
		Mortality: Change in DLCO over 6 months – 15% predicted :	1.6	1.1	2.5	0.470003629	0.20943381
		Mortality: Change in DLCO over 6 months – 20% predicted :	1.8	1.1	3.0	0.587786665	0.25594442
		Mortality: Change in DLCO over 6 months – 25% predicted :	2.3	1.2	4.2	0.832909123	0.31958239

Guideline section	Study ID	Outcome & Prognostic factor	RR/OR/HR	Lower CI	Upper CI	ln(RR/OR/HR)	SE (In RR RR/OR/HR)
		Mortality: Change in DLCO over 12 months – 10% predicted	2.2	1.4	3.5	0.78845736	0.23374764
		Mortality: Change in DLCO over 12 months – 15% predicted	2.3	1.5	3.7	0.832909123	0.2303234
		Mortality: Change in DLCO over 12 months – 20% predicted	3.0	1.8	4.9	1.098612289	0.25547157
		Mortality: Change in DLCO over 12 months – 25% predicted	3.5	2.0	6.1	1.252762968	0.2844749
	Zappala2010[507]	Decline in FVC at 6 months -adjusted for DLCO	3.33	1.61	6.88	1.202972304	0.37050624
		Progression free survival patients with 5-10% decline in FVC compared with stable disease-adjusted for baseline DLCO	2.56	1.17	4.38	0.940007258	0.33674617
Prognosis: Sub maximal exercise	DuBois2012A[4]	All-cause mortality: Baseline 6MWD	-	-	-	-	-

Guideline section	Study ID	Outcome & Prognostic factor	RR/OR/HR	Lower CI	Upper CI	ln(RR/OR/HR)	SE (ln RR RR/OR/HR)
testing		<250m vs. >/=350m					
		All-cause mortality: Baseline 6MWD 250-349m vs. >/=350m:	-	-	-	-	-
		All-cause mortality: 24 week change in 6MWD <-50m vs. >/=25m	-	-	-	-	-
Prognosis: Sub maximal exercise testing		All-cause mortality: 24 week change in 6MWD -50 to -26m vs. >/=25m	-	-	-	-	-
	Caminati 2009[53]	All-cause mortality: Baseline 6MWD	0.995	0.990	0.999	-0.005012542	0.00230863
		All-cause mortality: Change in 6MWD at 12 months	0.994	0.988	1	-0.006018072	0.00307974
	Hallstrand 2005[172]	All-cause mortality: Baseline 6MWD 30-m units change	0.91	0.81	1.02	-0.094310679	0.05880706
Pharmacological interventions	Panther2012[201]	Death from any cause	9.26	1.16	74.1	2.225704049	1.06045804
		Death from any cause or	3.74	1.68	8.34	1.319085611	0.4087422

Guideline section	Study ID	Outcome & Prognostic factor	RR/OR/HR	Lower CI	Upper CI	ln(RR/OR/HR)	SE (In RR RR/OR/HR)
		hospitalisation					
		Death from any cause or >/=10% decline in FVC	1.46	0.7	3.05	0.378436436	0.3754634
	Noth2012[359]	Primary endpoint	1.32	0.7	2.47	0.277631737	0.3216564
		All-cause mortality	4.85	1.38	16.99	1.578978705	0.64044424
		Combined all-cause mortality or non-elective, non-bleeding hospitalisations	2.12	1	4.52	0.751416089	0.38482449
		Combined all-cause mortality or >/=10% FVC drop	1.44	0.69	2.99	0.364643114	0.37406558

1

Appendix J: Costing of a Multidisciplinary Team (MDT) in the Context of an Interstitial Lung Disease (ILD) Network: Finding the incremental cost of involving an MDT in the IPF diagnostic pathway.

J.1 Introduction

The addition of the MDT to the diagnostic pathway will mean extra resources will need to be made available to enable staff to attend the MDT. In recognition that the specialist staff who form an MDT may be geographically widely distributed, the economic consideration of adding an MDT to the diagnostic pathway is undertaken with the assumption that MDTs will evolve within an ILD network configuration.

In an ILD network, we could assume that two forms of MDTs occur: a local level MDT in secondary care and a specialist level MDT in a tertiary care referral hub. The cost per IPF patient diagnosed through a network of MDTs will depend on the implementation costs and on the number of ILD patients (including IPF patients) diagnosed in the network.

The below sections propose a possible configuration for a network and estimate an incremental cost of £682 per IPF patient diagnosed with MDT involvement, or £227 per ILD (including IPF) diagnosis made. To note these estimated costs may cover up to one local and three tertiary MDT meetings as part of the diagnostic pathway. The costing assumes that there would be one specialist MDT and six local MDTs in each network, serving a population of 1.5 million. Other configurations may result in different cost per diagnosis.

J.2 Implementation costs of local and specialist level MDTs

J.2.1 The type, number and location of staff involved in local MDT meetings

It is envisioned that at a local MDT would consist of a radiologist and respiratory medical consultant as a minimum. Although there is potential involvement of a pathologist and ILD nurse (band 6), the costing does not include the time of these members as part of the local team, as it is envisioned they would be a shared resource across the network and included only as part of the specialist team.

J.2.2 The type, number and location of staff involved in specialist MDT meetings

It is envisioned that a specialist MDT would consist of a radiologist, chest physician and pathologist at consultant grade and with a specialist interest in ILD. A nurse with a specialist interest in ILD could also be present (band 6). Further, additional clerical staff could be employed to coordinate the MDTs at tertiary level and provide support for local level centres. The role of the administrative staff could include managing meetings, continuity of patient care, patient notes and potentially management of information for audit and research purposes.

J.2.3 Unit cost of staff and time involvement

The unit cost of each cadre of staff, alongside the cost of their time for their membership in an MDT meeting, is provided in Table 108. These meeting costs represent opportunity costs of the increased time commitment of already employed staff to the MDT; however, the unit cost where qualification has been incorporated is presented in parenthesis for information and in recognition that additional staffing levels may be needed.

We assume that a local MDT meeting, including any additional preparation time, will involve 3 hours for each clinical staff member. We assume local level MDT members are not present at specialist level MDTs, and no additional referral time is costed. We assume that a specialist MDT meeting, including any additional preparation time, will involve 2 hours for each clinical staff member. We have not taken into account the potential for staff members to have less than 100% attendance at MDT meetings. In a sensitivity analysis, the time per weekly specialist MDT was increased to 3 hours.

Depending on the configuration of the network it is possible some staff members will need to travel, the costs (including time) of which would be in part dependent on the distances involved between centres and the frequency and duration of the meetings. However, the potential to use of information technology and teleconference facilities may mitigate this need. Therefore, the time and cost of travel has not been considered further.

Table 108: Unit cost of MDT staff

Cadre of staff	Per contract hour	Per local MDT meeting	Per specialist MDT meeting	Annual cost per member of staff for local MDT meetings			Annual cost per member of staff for specialist MDT meetings			Source
				Number of meetings per year			Number of meetings per year			
				52	26	12	52	26	12	
Consultant (Medical, Radiologist, Pathologist)	£110	£330	£220	£17,160	£8,580	£3,960	£11,440	£5,720	£2,640	PSSRU (2010)[381]
With Qualification	£127	£381	£254	£19,812	£9,906	£4,572	£13,208	£6,604	£3,048	
Specialist respiratory nurse (band 6)	£28	£84	£56	£4,368	£2,184	£1,008	£2,912	£1,456	£672	PSSRU (2010)[381]
With Qualification	£31	£93	£62	£4,836	£2,418	£1,116	£3,224	£1,612	£744	
MDT coordinator - (Band 4 – agenda for Change point 16)	£13 (a)	£489	£489 (b)	£25,411	£25,411	£12,706	£25,411	£25,411	£12,706	Estimate (c)
With Qualification	£13	£489	£489	£25,411	£25,411	£12,706	£25,411	£25,411	£12,706	
MDT composition										
3 consultants, specialist nurse and MDT coordinator	£371	£1,563	£1,205	£81,259	£53,335	£25,594	£62,643	£44,027	£21,298	Calculated
With Qualification	£425	£1,725	£1,313	£89,683	£57,547	£27,538	£68,259	£46,835	£22,594	
3 consultants and MDT coordinator	£343	£1,479	£1,149	£76,891	£51,151	£24,586	£59,731	£42,571	£20,626	Calculated
With Qualification	£394	£1,632	£1,251	£84,847	£55,129	£26,422	£65,035	£45,223	£21,850	
2 consultants	£220	£660	£440	£34,320	£17,160	£7,920	£22,880	£11,440	£5,280	Calculated
With Qualification	£254	£762	£508	£39,624	£19,812	£9,144	£26,416	£13,208	£6,096	

(a) Per contract hour based on full annual salary plus on cost and 37.5 hour week.
(b) Per meeting cost based on full annual salary plus on cost divided by 52 meetings
(c) 52 meetings based on £21,176 annual salary with 20% employers on cost of £4235. 12 meetings based on 0.5 WTE of £21,176 per annum salary with 20% employers on cost.

Note: For information, cost estimates of staff time have been provided in full for information and completeness (as provided in development of the analysis). However, costs for staff not used in the costing are indicated in a lighter colour. For example the cost of an ILD specialist nurse or MDT coordinator was not included in the cost of a local MDT as their input is assumed only to be required for a specialist MDT.

Based on the unit costs presented in Table 108 and taking into account qualification, we could estimate the annual staff cost for weekly specialist MDTs (consisting of 3 consultants, a respiratory nurse and full time coordinator support) to be £62,643 (£1,351 per meeting with audio-visual included). If these meetings were monthly with coordinator support (0.5 WTE), the annual staff cost would be £22,594.

The annual staff cost for a *fortnightly* local MDTs consisting of only 2 consultants (i.e. a radiologist and chest physician) would be £19,812 (£785 per meeting with audio-visual included). The annual staff cost for *monthly* local MDTs consisting of only 2 consultants (i.e. a radiologist and chest physician) would be £9,144 (£812 per meeting with audio-visual included).

J.2.4 The availability and cost of teleconferencing facilities.

The cost of videoconferencing will depend in part on the type of system specified and the number of sites involved. Additional costs would include line rentals and potentially additional IT equipment. An additional consideration is whether further administrative support or training would be required in the operation of the teleconferencing facility and in preparing slides and papers for electronic distribution in a timely manner. The cost of the video conferencing system would depend on the number and type of inputs and outputs as well as the quality requirement. Dependent on these factors commercial quotes for medical audio-visual teleconferencing range from £10,000 to £30,000 per centre. However, with many centres already utilising MDTs for other conditions, rooms may already be set up for MDT purposes. In this case, where the ILD network could “piggy back” on capital and arrangements already made, running and installation costs could be as low as £1324 installation fee for the hub and £45 per month fee for each participating unit (Confidential communication with provider of audio-visual equipment to NHS, 2012). For the purposes of costing, we have allowed a budget of £600 per local centre and £2000 for the specialist centre to invest in audio-visual equipment per year.

J.2.5 The number of teams needed to serve the network and the configuration of MDTs within the network.

There is diversity and variation in the existing arrangements for MDTs and referral for the diagnosis of IPF patients. The incremental cost of adding an MDT into the diagnostic pathway is likely to vary depending on the existing architecture, the local incidence of IPF and potential best configuration (for instance, whether the MDTs at different levels are combined or done in isolation). However, in the sections below we use prevalence and incidence estimates, alongside assumptions of the role of the local and specialist MDTs, to provide a possible configuration of MDTs within the network for costing purposes.

In accordance with the information presented in sections below, we could assume that a network serves a population of 1.5 million. This network would have one specialist weekly MDT which would review 9 patients, of which 2 or 3 would be diagnosed with IPF. In order to achieve this number of referred patients per week, the network could consist of 6 local centres which would have fortnightly MDTs, reviewing 25 ILD patients per MDT (either to diagnose new cases or to discuss management plans). In any given month, it would be expected that a local MDT will need to refer an ILD patient to a specialist MDT to confirm diagnosis of IPF.

J.3 The population served by each MDT and across a network

J.3.1 Prevalence and incidence of IPF in the UK population.

It has been estimated that there are around 15,000 people in the UK with a diagnosis of IPF and each year 5000 new cases are identified. In 2010 the UK population was estimated to be 62.3 million (ONS 2011). This would give a prevalence estimate of 24 IPF patients per 100,000 population, with an expected 8 newly diagnosed cases per 100,000 per year.

J.3.2 The number of patients reviewed and managed by local level MDTs.

According to the population size a network serves, the below table gives estimates on the number of IPF and ILD patients (including IPF patients) that could present and be managed by the local centres within a network serving the population size specified. It is assumed that IPF patients form one third of the ILD patients presenting.

It is acknowledged that the role of the MDT may not purely be to diagnose ILD patients, but also to manage their care. Although this additional role of the MDT is outside of the scope of the guideline, it is considered due its potential to bring health benefit and to estimate the number of patients reviewed by the MDT on a weekly or monthly basis. For costing purposes, we therefore assume that local MDTs will be responsible for reviewing on the care management of all diagnosed ILD patients within their catchment area. We assume that, on average, an ILD patient's management plan is reviewed by their local MDT three times per year.

Table 109: The number of IPF and ILD (including IPF) patients reviewed and managed by local level MDTs

Size of population served by network	**Number of new IPF cases presenting in a network**			**Number of diagnosed IPF patients served by a network**			**Number of IPF patient management plans discussed** by local level MDTs in a network			**Total number of IPF patients discussed** by local level MDTs in a network		
a=annually m=monthly wk=weekly	**a**	**m**	**wk**	**a**	**m**	**wk**	**a**	**m**	**wk**	**a**	**m**	**wk**
62,000,000 (UK population)	5000	417	96	15, 000	1250	288	45, 000	3750	865	20, 000	1667	50, 000
100000	8	1	0	24	2	0	73	6	1	32	3	81
500000	40	3.4	1	121	10	2	363	30	7	161	13	403
750000	60	5	1	181	15	3	544	45	10	242	20	605
1000000	81	7	2	242	20	5	726	60	14	323	27	806
1500000	121	10	2	363	30	7	1089	91	21	484	40	1210
2000000	161	13	3	484	40	9	1452	121	28	645	54	1613
2500000	202	17	4	605	50	12	1815	151	35	806	67	2016
62,000,000	15, 000	1250	288	45, 000	3750	865	135, 000	11, 250	2596	150, 000	12, 500	2885
100000	24	2	0	73	6	1	218	18	4	242	20	5
500000	121	10	2	363	30	7	1089	91	21	1210	101	23
750000	181	15	3	544	45	10	1633	136	31	1815	151	35

Size of population served by network	**Number of new IPF cases presenting in a network**			**Number of diagnosed IPF patients served by a network**			**Number of IPF patient management plans discussed** by local level MDTs in a network			**Total number of IPF patients discussed** by local level MDTs in a network		
1000000	242	20	5	726	60	14	2177	181	42	2419	202	47
1500000	363	30	7	1089	91	21	3266	272	63	3629	302	70
2000000	484	40	9	1452	121	28	4355	363	84	4839	403	93
2500000	605	50	12	1815	151	35	5444	454	105	6048	504	116

Note: Population of 1.5 million assumed in the base case and highlighted in bold above.

The number of centres within a network will determine how many patients would be reviewed in an MDT. Given the assumptions and figures outlined above, the below table gives estimates of how many patients may be reviewed per month per local centre according to the number of centres in the network.

Table 110: Number of patients reviewed monthly by each local centre in the network according to the population size served by a network and the number of local centres within a network

Size of population served by network	**Number of patients reviewed monthly by each local centre in the network**					
Number of centres in the network	**3**	**4**	**5**	**6**	**7**	**8**
62,000,000	4167	3125	2500	2083	1786	1563
100000	7	5	4	3	3	3
500000	34	25	20	17	14	13
750000	50	38	30	25	22	19
1000000	67	50	40	34	29	25
1500000	101	76	60	50	43	38
2000000	134	101	81	67	58	50
2500000	168	126	101	84	72	63

Note: Population of 1.5 million assumed in the base case and highlighted in bold above.

J.3.3 The number of patients reviewed and diagnosed by specialist MDTs.

To undertake the costing, we assume that the specialist MDT meets with a purpose to diagnose ILD patients only. As such, the specialist MDT is not expected to spend time on the review of patients care and management. We assume that any patient with IPF will need to have their diagnosis confirmed at a specialist MDT. However, for the purposes of costing the MDT we assume that not all ILD patients will need to be referred to a specialist MDT for correct diagnosis and that 60% of ILD patients without IPF will be diagnosed at local level. This compares with an estimated 38% of ILD patients that have IPF excluded as a diagnosis at local level in the analysis presented in appendix K. This percentage is calculated by using the sensitivity and specificity of clinical and radiological findings estimated from data presented by Flaherty (2007) and colleagues[152], and the assumption that 8% of patients with an unconfident diagnosis of IPF through a HRCT will have IPF excluded from their diagnosis with a bronchoalveolar lavage (BAL)[365] (please see appendix K for further detail). In a

sensitivity analysis, the time requirement of the weekly specialist MDT was increased from 2 to 3 hours, to take into account that local expertise and level of referral.

It is possible that a specialist MDT could need to review the diagnosis of a patient up to three time to confirm a diagnosis (i.e. to decide the need for bronchoaveolar lavage or transbronchial biopsy, to interpret the results of the biopsy and consider the need for further surgical biopsy and then if applicable to interpret the results of surgical biopsy). For the purposes of costing the MDT using the clinical experience of the GDG we assume that:

- 70% of patients are reviewed by specialist MDT only one time (i.e. biopsy is not needed or inappropriate)
- 25% of patients are reviewed by specialist MDT two times (i.e. the patient has required one biopsy)
- 5% of patients are reviewed by specialist MDT three times (i.e. the patient has required two biopsies)

If we use the sensitivity and specificity for the diagnostic interventions as extracted for the clinical review from Flaherty (2007)[152], Ohshimo (2009)[365], Flaherty (2002) [150]and Coutinho (2008)[89] we could estimate 53% of patients are diagnosed with clinical exam and HRCT, 43% of patients are diagnosed after a first biopsy, and 4% of patients are diagnosed with a final surgical lung biopsy (please see appendix K for further detail).

Table 111: Number of patients reviewed at specialist level MDT according to size of population served by a network.

Size of population served by network	Number of patients referred weekly to specialist MDT	Number of patients on 2nd review	Number of patients on 3rd review	Total number of patients reviewed at weekly meeting	Number of ILD patients diagnosed per week	Number of IPF patients diagnosed per week	Approximate number of specialist MDTs needed to serve UK population.
62000000	231	115	23	369	231	96	1
100000	0	0	0	1	0	0	620
500000	2	1	0	3	2	1	124
750000	3	1	0	4	3	1	83
1000000	4	2	0	6	4	2	62
1500000	6	3	1	9	6	2	41
2000000	7	4	1	12	7	3	31
2500000	9	5	1	15	9	4	25

Note: Population of 1.5 million assumed in the base case and highlighted in bold above.

J.4 Summary

Based on the above information, we could argue a potential configuration for an ILD MDT network configuration in the UK as follows:

Those 41 networks across the UK could serve a population of 1.5 million each. Each network would have one specialist weekly MDT which would review 4 to 5 patients, of which 2 to 3 patients would be diagnosed with IPF. In order to achieve this number of patients per week, the network could consist of 6 local centres which would have fortnightly MDTs, reviewing 25 ILD patients per MDT (either to diagnose new cases or to discuss management plans). Each local MDT would serve a population of approximately 250,000. In any given month, it would be expected that a local MDT will need to refer four ILD patients to a specialist MDT to confirm diagnosis.

The annual opportunity cost of MDT staff across such a network would be approximately £187,131 (£68,259 for weekly specialist MDTs and £118,872 for fortnightly local MDTs in 6 local centres). However, if we were to assume that local MDTs only spent 10 percent of time on diagnostic activity, the opportunity of staff time per year would be £80,146. When an additional cost of audio-visual is also accounted for, the total annual cost rises to £192,731 or £82,506 when considering diagnostic time only.

With 121 new presentations of IPF expected annually within the network, the incremental cost of running an ILD network of MDTs per IPF diagnosis would be approximately£682; or £227 per ILD (including IPF) diagnosis made. This assumes that the MDT has a hundred percent diagnostic yield.

It is important to note that these are estimates for only one form of network configuration and composition, with an assumption that 60% of ILD patients without IPF could be diagnosed at local level. If less patients can be diagnosed at local level, the time requirement and cost of the specialist MDT would increase If 3 hours was allowed for the specialist MDT instead of 2, the additional cost per ILD (including IPF) patient diagnosed through MDT discussion would rise to £286.The incremental cost would increase if the ILD network could not use facilities already in place for the cancer network that utilises an MDT approach. It is likely that the most cost effective configuration will depend on local need and commissioning arrangements.

Appendix K: Placing the diagnostic clinical evidence into an economic framework for decision making.

K.1 Introduction

An economic model to assess the cost effectiveness of diagnostic interventions for IPF was not prioritised in this guideline; in part this was due to the fact that treatment pathways that follow a correct diagnosis are still emerging and uncertain. As such the health benefit that could be obtained from a correct diagnosis of IPF and the opportunity cost of an incorrect diagnosis would also be uncertain. However, placing the clinical evidence in an economic framework for analysis can allow estimation of the number of correct and incorrect diagnoses that result from a diagnostic strategy. From these estimations it is possible to demonstrate which potential diagnostic strategies may create fewer successful diagnostic outcomes than others. In addition, when the outcome of a diagnostic strategy is considered alongside its cost, it is possible to demonstrate that some strategies are less successful but more costly – that is to say they are dominated options and should not be recommended on the grounds of cost effectiveness.

K.1.1 Population

The population considered in the analysis are ILD patients presenting within a diagnostic ILD network assumed to have a population of 1.5 million. We assume IPF patients form one third of all ILD patients presenting within the network, and on this basis estimate that there will be approximately 121 new presentations per annum. We assume all of the starting population is fit enough to biopsy.

K.1.2 The comparators

Eight diagnostic strategies are compared in the analysis. These strategies are based on four scenarios, as outlined below. Each scenario was considered with and without MDT involvement.

Scenario 1: Clinical examination (including PFTs) and HRCT only.

Scenario 2: Clinical examination (including PFTs) and HRCT, with the addition of BAL for any patients which could not have a confident diagnosis using HRCT findings.

Scenario 3: Clinical examination (including PFTs) and HRCT, with the addition of BAL for any patients which could not have a confident diagnosis using HRCT findings. Where BAL could not exclude IPF with certainty, these patients would have a biopsy. That is to say only patients which had an unconfident diagnosis would be referred for biopsy.

Scenario 4: Clinical examination (including PFTs) and HRCT, with the addition of BAL for any patients which could not have a confident diagnosis using HRCT findings. With the exception of patients that were diagnosed with an alternative ILD at BAL, all patients have a biopsy to confirm diagnosis of HRCT.

K.2 Clinical Effectiveness inputs in the primary analysis

The analysis is based on clinical evidence identified in the diagnostic systematic review undertaken for the guideline, supplemented by additional data sources as required. A summary of the inputs used in the base-case (primary) analysis is provided in the table below.

Table 112: Inputs to estimate diagnostic accuracy of interventions in the diagnostic pathway in the base-case analysis

Intervention		Value	Source	Notes
Clinical examination and HRCT				
Confident diagnosis	Sensitivity	67%	Calculation using data presented by Flaherty (2007)	MDT final agreement used as reference standard. All questionable cases are excluded in the calculation. Calculation used data from community and academic clinicians and radiologists.
	Specificity	89%		
Unconfident diagnosis	Specificity	58%	Calculation using data presented by Flaherty (2007)	MDT final agreement used as reference standard. All questionable cases are included in the calculation. Calculation used data from community and academic clinicians and radiologists.
	Specificity	82%		
Clinical examination and HRCT + MDT				
Confident diagnosis	Sensitivity	92%	Calculation using	MDT final agreement used as

Intervention		Value	Source	Notes
	Specificity	94%	data presented by Flaherty (2007)	reference standard. All questionable cases are excluded in the calculation. Calculation used data from community and academic clinicians and radiologists.
Unconfident diagnosis	Sensitivity	76%	Calculation using data presented by Flaherty (2007)	MDT final agreement used as reference standard. All questionable cases are included in the calculation. Calculation used data from community and academic clinicians and radiologists.
	Specificity	67%		
Bronchoalveolar lavage (BAL)				
Percentage of IPF cases confirmed at HRCT that will be rediagnosed as not having IPF with BAL		8%	Ohshimo (2009)	This percentage applies to the total number diagnosed with IPF at HRCT, but is only composed of the false positives
Percentage of cases suspected without IPF, confirmed negative with BAL		25%	Expert opinion	This percentage applies to the total number diagnosed without IPF at HRCT, but is only composed of the true negatives
Accuracy of biopsy after clinical exam, HRCT.				
After a confident HRCT diagnosis	Sensitivity	96%	Calculation using data presented by Flaherty (2007)	MDT final agreement used as reference standard. All questionable cases are excluded in the calculation. Calculation used data from community and academic pathologists.
	Specificity	72%		
After an unconfident HRCT diagnosis	Sensitivity	88%	Calculation using data presented by Flaherty (2007)	MDT final agreement used as reference standard. All questionable cases are included in the calculation. Calculation used data from community and academic pathologists.
	Specificity	59%		
Accuracy of biopsy after clinical exam, HRCT + MDT				
After a confident HRCT diagnosis	Sensitivity	99%	Calculation using data presented by Flaherty (2007)	MDT final agreement used as reference standard. All questionable cases are excluded in the calculation. Calculation used data from community and academic pathologists.
	Specificity	89%		
After an unconfident HRCT diagnosis	Sensitivity	85%	Calculation using data presented by Flaherty (2007)	MDT final agreement used as reference standard. All questionable cases are included in the calculation. Calculation used data from community and academic pathologists.
	Specificity	71%		
Probability that diagnosis will be confident at clinical exam and HRCT				
when patient has IPF		74%	Calculated from	

Intervention		Value	Source	Notes
when patient has not got IPF		38%	Hunninghake (2007)	

K.3 Analytical Overview

K.3.1 Placing the clinical effectiveness data into an analytical framework

Using the inputs identified by systematic review and listed above, a series of 2 by 2 tables were constructed for each intervention in the diagnostic pathway to calculate the number of true positives, true negatives, false negatives and false positives that could be expected for each scenario. Those constructed for the diagnostic pathway without MDT involvement are depicted in Figure 113 and Figure 114; however the exact same structure was used for the pathway with MDT involvement. The figures in the table have been rounded to 2 decimal places as calculated by the pathway; however, for explanatory purposes the text below explains the figures in whole numbers which may differ slightly due to rounding error.

To note, the information shown in Figure 114 shows the level of agreement between the diagnosis by clinical exam and HRCT, and the diagnosis made by biopsy. So for example, 60 patients were correctly and confidently diagnosed with IPF by HRCT, and subsequent biopsy would correctly diagnose a further 26 patients, and as such assumed to be in agreement in 60 true positive cases. HRCT correctly and confidently diagnosed 81 patients to not have IPF, whereas a biopsy only correctly diagnosed 66 patients to not have IPF, therefore HRCT and biopsy agreed 66 true negative cases. Further HRCT and biopsy agreed in 3 false negative cases and 10 false positive cases (i.e. both interventions diagnosed incorrectly).

Therefore in patients where a confident diagnosis was made by HRCT, the biopsy agrees with the diagnostic conclusion in 138 out of 181 cases (77%). In the other 43 cases HRCT and biopsy will disagree and the diagnosis will be uncertain. The level of agreement is affected by the prior prevalence of disease, as the two tests could come to the same conclusion by chance. Therefore, for information the kappa statistic was calculated to measure interobserver agreement. So for instance when HRCT findings are confident, the level of agreement adjusting for chance is 0.56 (the kappa statistic).

The pathway allowed four different scenarios to be explored.

The first scenario is that where the patient is only offered a HRCT scan. It considered only the outcomes from the 2 by 2 tables constructed for the confident and unconfident HRCT. These tables can be seen in Figure 113.

The second scenario is that where the patient is offered a HRCT scan, and if the diagnosis is unconfident they are then offered BAL. Scenario 2 considered only the outcomes seen in the 2 by 2 table constructed for confident HRCT findings and those after BAL had been performed on patients with unconfident HRCT findings. These tables can be seen in Figure 113

The third scenario is that where the patient is offered a HRCT scan, and if the diagnosis is unconfident is offered BAL to rule out IPF. Those which are not ruled out with BAL are offered biopsy. This scenario considered the outcomes seen in the 2 by 2 table constructed for confident HRCT findings and the patients which had left the pathway after BAL (i.e. patients which BAL confirmed as true negatives). In addition this scenario considered the outcomes in the 2 by 2 table constructed using the cases where uncertain HRCT findings and biopsy agreed or disagreed, as shown in Figure 114.

The fourth scenario is that where every patient is offered an additional diagnostic procedure after HRCT. If the diagnosis is confident at HRCT, the patient is offered biopsy to confirm. If the diagnosis is unconfident at HRCT, the patient is offered BAL to rule out IPF, and if IPF is still suspected is offered biopsy. This scenario considered the patients which had left the pathway after BAL (as seen in Figure 113) as well as the outcomes in the 2 by 2 table constructed using the cases where uncertain and certain HRCT findings and biopsy agreed or disagreed (as shown in Figure 114).

When only HRCT or BAL was considered in the pathway (scenarios 1 and 2), the outcomes were to be diagnosed with or without IPF, either correctly or incorrectly. When biopsy was considered as an additional step (scenarios 3 and 4), there was also the possibility of an uncertain diagnosis as an outcome (whereby HRCT and biopsy disagreed). The outcomes for each of the scenarios with MDT involvement were considered in the same manner as described above.

Figure 113: The first stages of the diagnostic pathway, without MDT involvement.

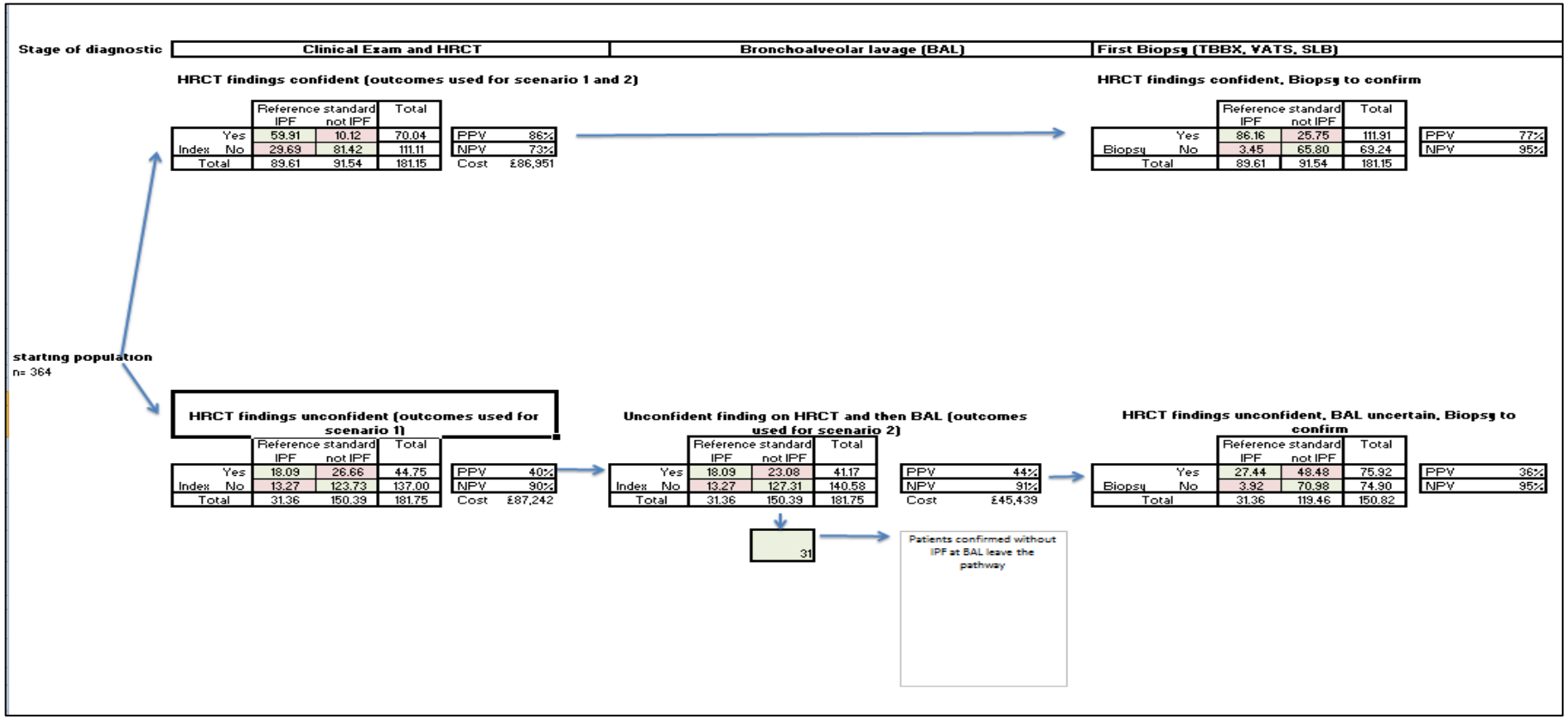
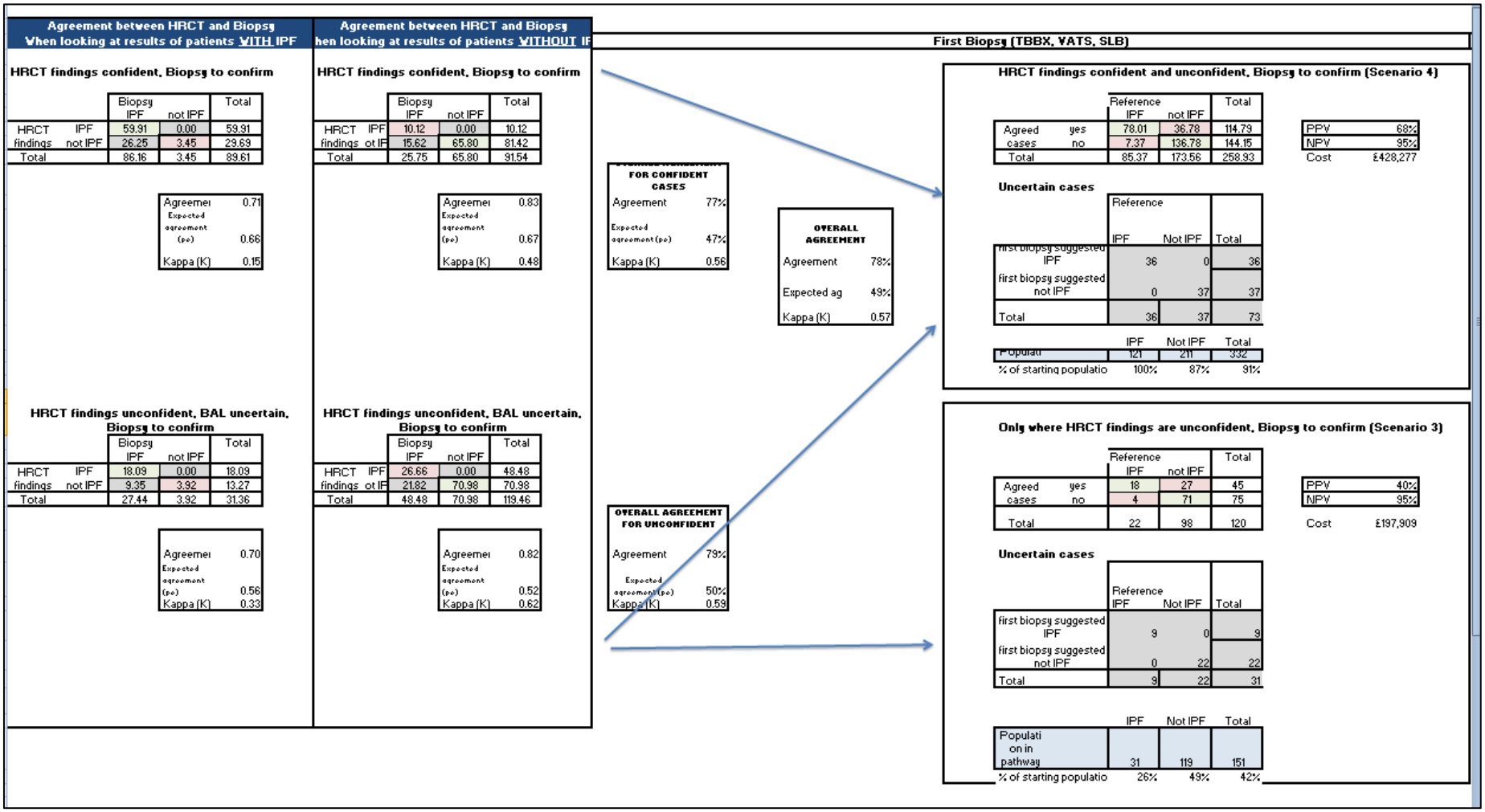


Figure 114: The level of agreement between the diagnostic conclusion of the HRCT and biopsy (post HRCT) which would be found with no MDT involvement.



1

K.4 Calculating the cost of each diagnostic strategy

From the series of 2 by 2 tables, the number of patients undertaking each diagnostic intervention in both the pathways with and without MDT involvement could be calculated. To find the total cost of diagnostic pathway in each scenario, the unit cost of each diagnostic intervention was multiplied by the number of patients having the intervention. The cost of staff time was used to estimate the cost of the MDT, with the cost of audiovisual equipement is incorporated in the cost of a specialist MDT .

To incorporate the cost of MDT involvement in the diagnostic model, the assumption is made that everyone entering the pathway is fit enough to benefit from biopsy. This differs from the approach used in the MDT costing presented Appendix J where clinical members considered the likelihood of being fit enough to biopsy in their estimate of the likelihood of being reviewed more than once by a specialist MDT.

With the assumption that everyone entering the pathway is fit enough to benefit from biopsy, the proportion of patients being reviewed by a local MDT or specialist MDT can be derived by the diagnostic pathways. In scenario 1, every patient has a HRCT but no further intervention, therefore the patient is reviewed once by a local level MDT. In scenario 2, every patient has a HRCT and a proportion with a confident diagnosis will be diagnosed at local level MDT – the remainder will be reviewed by a specialist level MDT (i.e. with a pathologist) before BAL and post BAL. In the third scenario, again a proportion will have a confident diagnosis at local level MDT – the remainder will be reviewed by a specialist MDT (i.e. with a pathologist) before BAL and post BAL, and in some cases post biopsy where applicable. In the fourth scenario, every patient will be reviewed at least one review by a specialist MDT as every patient undergoes BAL or biopsy (mirroring the assumption made in the MDT costing outlined in Appendix J. The number of diagnostic patient reviews at each level is therefore dependent on the assumptions made in the scenario and the accuracy/level of confidence at each stage in the pathway.

The table below also details the number of patients that require a diagnostic review per monthly MDT meeting at a local level, or at a weekly meeting at a specialist level. This was calculated based on the number of patients requiring a diagnostic review given the incidence of IPF within a network of 1.5 million.

Table 113: Data generated from and used in costing of MDT diagnostic pathways

	Scenario			
	1	**2**	**3**	**4**
% of IPF patients which are diagnosed at local level	100%	74%	74%	0%
% of non IPF patients which are excluded at local level	100%	38%	38%	0%
% of all patients diagnosed at local level	100%	50%	50%	0%
Of those patients who have not been diagnosed at local level				
% of patients which are reviewed three times by specialist MDT	0%	0%	86%	93%
% of patients which are reviewed twice by specialist MDT	0%	100%	14%	7%
% of patients which are reviewed once by specialist MDT (%)	0%	0%	0%	0%
Number of diagnostic reviews undertaken in an MDT				
In one local MDT per month	50	50	50	50
In one specialist MDT per week (including first, second and third reviews)	0	9	13	27

TOTAL - Annual cost of local MDT spent on diagnosis (10% of time on diagnosis)	***£13,658***	***£11,887***	***£11,887***	***£11,887***
TOTAL – annual cost of specialist weekly meetings (100% of time allocated spent on diagnosis)	***£0***	***£133,385***	***£178,978***	***£337,410***

By using the data in Table 113, it is possible to calculate the expected cost of MDT involvement with each scenario, by multiplying the number of diagnostic reviews undertaken in each MDT by the unit cost of the staff involved at each MDT. Each local level diagnostic review was expected to take 8 minutes on average, and each specialist level diagnostic review (including preparation time) was expected to take 32 minutes, as calculated by the MDT costing presented in Appendix J. This was thought reasonable by clinical members of the group given that at local level there would be some less complex cases which would require minimal discussion and that at specialist level more preparation time may be required. However, this assumption was tested in a sensitivity analysis where the time assigned to a patient review in a local MDT was increased to 15 minutes, and reduced to 15 minutes in the specialist MDT.

Table 114 presents the costs associated with each level of MDT in each scenario. Please note that scenario 1 does not include the cost of a specialist MDT, as biopsy is not offered in this scenario. However, 0.5 WTE of clerical support has been included as a means of facilitating local MDT arrangements. The overall cost of MDT involvement is higher than that reported in the MDT costing in Appendix J as we have assumed all patients are fit to biopsy, and therefore the time requirement of the specialist MDT staff has increased. The annual cost of local and specialist MDT involvement was added to the cost of the other diagnostic interventions for that scenario, as shown in Table 115.

Table 114: The cost of local and specialist level MDTs in each scenario.

	Scenario			
	1	**2**	**3**	**4**
Local or community MDT (1 clinician and 1 radiologist)				
Annual cost of clinical MDT staff in local MDT across network	£118,872	£118,872	£118,872	£118,872
Annual cost of support staff (if no specialist centre 0.5 WTE of clerical support is assigned)	£12,706	£0	£0	£0
Annual cost of audio - visual (if no specialist centre, one of the local centres act as a hub)	£5,000	£3,600	£3,600	£3,600
Specialist MDT (1 clinician, 1 radiologist, one pathologist)				
Annual cost of clinical staff at specialist meetings (including 1 ILD nurse and 3 consultants)	£0	£105,974	£151,567	£309,999
Annual cost of support staff at specialist meeting	£0	£25,411	£25,411	£25,411
Annual cost of audio - visual (if no specialist centre, one of the local centres act as a hub)	£0	£2,000	£2,000	£2,000
Total annual cost of MDT time spent on diagnosis	£13,658	£145,272	£190,865	£349,297

Note: These costs were calculated by multiplying the unit cost of an MDT (as estimated in Appendix J by the number of patients being reviewed (as calculated in table 6).

Table 115: The annual cost and number of ILD patients per network expected to have a diagnostic intervention in each scenario's diagnostic strategy.

Intervention	Unit cost (a)	Scenario 1		Scenario 2		Scenario 3		Scenario 4	
		Number of patients (b)	Cost (a * b)	Number of patients (c)	Cost (a * c)	Number of patients (d)	Cost (a * d)	Number of patients (e)	Cost (a * e)
Diagnostic pathway without MDT involvement									
Clinical exam and HRCT	£480	363	£174,194	363	£174,194	363	£174,194	363	£174,194
BAL	£250			182	£45,439	182	£45,439	182	£45,439
Biopsy	£1,654					151	£249,458	332	£549,078
Total annual cost		£174,194		£219,632		£469,090		£768,710	
Diagnostic pathway with MDT involvement									
Clinical exam and HRCT	£480	363	£174,194	363	£174,194	363	£174,194	363	£174,194
BAL	£250			182	£45,439	182	£45,439	182	£45,439
Biopsy	£1,654					156	£258,671	338	£558,293
Annual cost of local level MDT			£13,658		£11,887		£11,887		£11,887
Annual cost of specialist level MDT					£133,385		£178,978		£337,410
Total annual cost		£187,851		£364,904		£669,170		£1,127,222	

Note: The number of patients displayed in this table is based on the number of ILD patients expected to present annually within an ILD network that serves a population of 1.5 million. The unit cost is based on the costing presented in appendix J and NHS reference costs[107]

K.4.1 Estimation of the health benefit of the diagnostic outcomes

The outcome of a diagnostic strategy can be placed in four categories: true positives (IPF patients correctly diagnosed with IPF), true negatives (ILD patients without IPF correctly excluded of an IPF diagnosis), false negatives (IPF patients incorrectly excluded of an IPF diagnosis) and false positives (ILD patients without IPF incorrectly being diagnosed with IPF). The health benefit and cost associated with each of these outcomes in the IPF population is not known, as effective management of IPF are still emerging and are uncertain. However, the potential consequences of the various diagnostic outcomes should be given due consideration. One means of doing so is by attaching a hypothetical Quality Adjusted Life Year to each outcome and explore how the impact of changing the QALY associated with each outcome influences the results of the analysis.

The below table gives a qualitative summary of the potential consequences of each diagnostic outcome, and details the QALY given to each diagnostic outcome found in the analyses. To note, the downstream cost which could be required to achieve the downstream health benefit has not been considered further in the analysis, and therefore the results should be interpreted with caution.

Table 116: Estimation of the health benefit which could be found with each diagnostic outcome.

Diagnostic Outcome	Potential downstream cost and health benefit	Hypothetical QALY associated with each diagnostic outcome			
		Base case analysis (a)	Sensitivity Analysis 1(b)	Sensitivity Analysis 2 (c)	Sensitivity Analysis 3 (d)
True positives	• Timely IPF management plan with health benefit (QoL) • Utility of correct prognosis	+0.08 QALY	+ 0.7 QALY	+0.7 QALY	0
True negatives	• Possible diagnosis of alternative condition with health benefit of appropriate management • Appropriate onward referral and associated benefit (outside scope)	+0.08 QALY	+0.7 QALY	+0.7 QALY	+0.7 QALY
False negatives	• Delayed diagnosis of IPF with possible less effective management options (i.e. reduced QoL for longer time) • Inappropriate onward referral, further investigative tests	-0.08 QALY	-0.7 QALY	0	0
False positives	• Patients with conditions other than IPF may miss out on health benefit of alternative treatment • Patient "disutility" of incorrect prognosis for other patients	-0.08 QALY	-0.7 QALY	0	0

(a) 0.08 is the minimally important difference used in this guideline for a quality of life improvement. In this analysis we assume that a correct diagnosis will improve the quality of life of an ILD patient for one year.

(b) In this analysis we assume a correct diagnosis gives an IPF patient one additional year of life of 0.7. This could be reflective of a future scenario whereby effective treatment for IPF becomes available. We assume that other ILD patients will also benefit to the same extent by having a correct diagnosis.

(c) As above, however we assume that incorrectly diagnosed patients do not have a decreased health benefit to if their diagnosis remains uncertain.

(d) As above, however we assume that only the ILD patients have a substantial health benefit from a correct diagnosis.

K.5 Dealing with uncertainty in the estimates of diagnostic accuracy of interventions in the pathway.

In order to take into account the range of estimates of the accuracy of the interventions in the diagnostic pathway, a univariate sensitivity analysis was conducted where the estimates of accuracy of each intervention in the pathway were systematically replaced with the alternative estimates of accuracy as reported by the clinical review. In each sensitivity analysis, costs and downstream health benefits remained the same as those used in the base case analysis. The accuracy estimates used in each analysis are reported in Table 117.

Table 117: The inputs of each of the univariate sensitivity analysis

Intervention		Value	Source	Notes
SA4: Clinical examination and HRCT				
Confident and unconfident diagnosis	Sensitivity	67%	Coutinho (2008)	Biopsy used as reference
	Specificity	90%		
SA5: Clinical examination and HRCT				
Confident and unconfident diagnosis	Sensitivity	71%	Peckham (2004)	Biopsy used as reference
	Specificity	67%		
SA6: Clinical examination and HRCT + ATS guidelines				
Confident and unconfident diagnosis	Sensitivity	71%	Peckham (2004)	Biopsy used as reference
	Specificity	75%		
SA7: Clinical examination and HRCT of referral centre				
Confident diagnosis	Sensitivity	93%	Hunninghake (2001)	Pathologist core used as reference
	Specificity	36%		
Unconfident diagnosis	Sensitivity	64%		
	Specificity	48%		
SA8: Using data from Thomeer (2009) and Slodkowska (2000)				
Clinical examination and HRCT (confident and unconfident diagnosis at HRCT)	Sensitivity	92%	Thomeer (2009)	Based on the assumption that all patients recruited in the IFIGENIA trial had IPF. Specificity could not be calculated and therefore assumed the same as sensitivity
	Specificity	92%		
Biopsy After a confident diagnosis at HRCT	Sensitivity	84%		
	Specificity	84%		
Biopsy After an unconfident diagnosis at HRCT	Sensitivity	50%	Slodkowska (2000)	Pathologists in this study did not have access to HRCT results and therefore used as a proxy to accuracy where HRCT findings are
	Specificity	50%		

Intervention		Value	Source	Notes
				unconfident. Specificity could not be calculated and therefore assumed the same as sensitivity
SA9: Clinical exam, HRCT and Biopsy				
Biopsy After a confident diagnosis at HRCT	Sensitivity	63%	Flaherty (2002)	All patients assumed IIP, SLB + HRCT, but this is not clearly reported in paper. Specificity could not be calculated and therefore assumed the same as sensitivity
	Specificity	63%		
Biopsy After an unconfident diagnosis at HRCT	Sensitivity	50%	Slodkowska (2000)	Pathologists in this study did not have access to HRCT results and therefore used as a proxy to accuracy where HRCT findings are unconfident. Specificity could not be calculated and therefore assumed the same as sensitivity
	Specificity	50%		

K.6 Examining the effect of community versus academic clinical staff in the diagnostic pathway.

Flaherty et al (2007) provided patient level data which showed the frequency at which a clinician, radiologist and pathologist would amend their diagnosis post an MDT consensus. Data was disaggregated according to whether the consultant worked in a community or academic setting. Using the MDT consensus as a reference standard, it was possible to calculate the sensitivity and specificity of the radiologist and clinician, or pathologist, in obtaining the diagnosis eventually arrived by MDT consensus in both a community setting and an academic setting. In a sensitivity analysis this data is explored further to examine the impact the setting in which the consultant works may have on their accuracy of diagnosis. To note all other inputs, including all unit costs, remained the same as the base-case.

Table 118: Diagnostic accuracy estimates derived for community and academic clinical staff

Intervention		Value	Notes
Community setting - Clinical examination and HRCT			
Confident diagnosis	Sensitivity	78%	Calculation used data from community clinicians and radiologists only.
	Specificity	80%	
Unconfident diagnosis	Sensitivity	71%	
	Specificity	70%	
Academic setting - Clinical examination and HRCT			
Confident diagnosis	Sensitivity	60%	Calculation used data from academic clinicians and radiologists only.
	Specificity	95%	
Unconfident diagnosis	Sensitivity	49%	
	Specificity	90%	
Community setting - Clinical examination and HRCT, + MDT			
Confident diagnosis	Sensitivity	89%	Calculation used data from community clinicians and radiologists only.
	Specificity	83%	
Unconfident diagnosis	Sensitivity	87%	

Intervention		Value	Notes
	Specificity	66%	
Academic setting - Clinical examination and HRCT, +MDT			
Confident diagnosis	Sensitivity	94%	Calculation used data from academic clinicians and radiologists only.
	Specificity	96%	
Unconfident diagnosis	Sensitivity	69%	
	Specificity	91%	
Community setting - Accuracy of biopsy after clinical exam and HRCT.			
After a confident HRCT diagnosis	Sensitivity	92%	Calculation used data from community pathologists only.
	Specificity	53%	
After an unconfident HRCT diagnosis	Sensitivity	90%	
	Specificity	43%	
Academic setting - Accuracy of biopsy after clinical exam and HRCT.			
After a confident HRCT diagnosis	Sensitivity	98%	Calculation used data from academic pathologists only.
	Specificity	81%	
After an unconfident HRCT diagnosis	Sensitivity	86%	
	Specificity	67%	
Community setting – Accuracy of biopsy after clinical exam and HRCT + MDT.			
After a confident HRCT diagnosis	Sensitivity	100%	Calculation used data from community pathologists only.
	Specificity	78%	
After an unconfident HRCT diagnosis	Sensitivity	95%	
	Specificity	59%	
Academic setting – Accuracy of biopsy after clinical exam and HRCT + MDT.			
After a confident HRCT diagnosis	Sensitivity	98%	Calculation used data from academic pathologists only.
	Specificity	94%	
After an unconfident HRCT diagnosis	Sensitivity	80%	
	Specificity	71%	

Source/Note: Calculation using data presented by Flaherty (2007). MDT final consensus was used as a reference standard. For confident HRCT diagnosis, all questionable cases which final MDT could not make a firm diagnosis were excluded from the calculation. For unconfident HRCT diagnosis, all questionable cases which final MDT could not make a firm diagnosis were included in the calculation.

K.7 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs/QALYs(X) = total costs/QALYs for option X

- Cost-effective if: ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of two other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Benefit(X) = (QALYs\ (X) \times \lambda) - Costs\ (X)$$

Where: Costs/QALYs(X) = total costs/QALYs for option X; λ = threshold

- Cost-effective if: highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

Results are also presented graphically where total costs and total QALYs for each diagnostic strategy are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

K.7.1 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several interventions, we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained.

K.8 Results and interpretation of the analysis

The result of the base case analysis is given in Table 119 and represented graphically in Figure 115. The base-case results show that the only non-dominated strategies are scenario 1 with MDT, scenario 2 with MDT, scenario 3 with MDT, and scenario 4 with MDT. Using a cost effectiveness threshold of £20,000, the base case analysis suggests the most likely cost effective option is to have a clinical exam, PFTs, and HRCT with a multidisciplinary discussion at local level (scenario 1 with MDT). Varying the time required to review a patient in a local MDT and specialist MDT to 15 minutes respectively did not change the conclusions of the results (see Table 120). However, care should be taken when interpreting the results as the true QALY associated with each outcome is unknown, and further no downstream costs that would follow a diagnostic outcome have been incorporated into the analysis.

Table 121 gives the results of the sensitivity analyses where the value of the QALYs associated with each diagnostic outcome varied. Table 122 gives the results of the sensitivity analyses where estimates of diagnostic accuracy of various interventions in the pathway were replaced by alternative estimates derived by the clinical review. The results show that scenario 3 without MDT and scenario 4 without MDT remained dominated options in all of these sensitivity analyses. It is therefore unlikely these strategies are cost effective.

Table 123 show results of the sensitivity analysis where the setting in where the diagnostic clinical staff worked was considered. It shows that staff working in academic settings achieve greater diagnostic success than those working in the community both with and without an MDT. Scenarios with an academic MDT in this analysis dominate scenarios without MDT or community MDT. A limitation, however, is that any potential difference in staff costs between the academic or community setting were considered. Therefore the results of this analysis are only informative if the additional expertise of academic staff compared to community staff can be achieved with no additional cost to the NHS.

No analysis suggested that a strategy with biopsy was optimal. However, if a greater QALY gain could be associated with a correct diagnostic outcome; or alternatively a greater QALY or monetary loss could be associated with an incorrect diagnostic outcome, strategies involving biopsy would become more cost effective. It is worth noting that scenario 4, where everyone was offered biopsy post HRCT, ranked less optimal than scenario 3 in all analyses when using a threshold of £20,000. This gives greater strength to the argument that if biopsy is considered, it should only be offered to patients who have an unconfident diagnosis at HRCT. Also to note that scenarios with biopsy appeared more cost effective with MDT involvement than without, as MDT involvement reduced the number of cases where findings did not agree with HRCT findings.

A key limitation of this analysis is that it does not explore the impact of downstream costs associated with each diagnostic outcome. The addition of downstream cost is likely to further accentuate the patterns already seen in the analysis, as there is likely to be a greater cost to the NHS is associated with incorrect diagnoses. However, the findings of this analysis may not be reflective of a scenario where there is substantial cost associated with effective treatment of IPF patients. The cost effectiveness of diagnostic interventions is in part dependent on the cost effectiveness of the management strategies that follow a particular diagnostic result. A further consideration is that the analyses did not explore a QALY gain or loss associated to cases where no agreement.

K.9 Conclusion = Evidence Statement

It is likely that involvement of a multidisciplinary team at each stage of the diagnostic pathway for IPF patients is cost effective when compared to no involvement. This is based on evidence with direct applicability but with potentially serious limitations.

It is likely that with the involvement of a multidisciplinary team at each stage of the diagnostic pathway a diagnosis using clinical and radiological findings alone is more cost effective than a diagnosis using clinical and radiological findings with biopsy. This is based on evidence with direct applicability but with potentially serious limitations.

Table 119: Results of the base case analysis

Scenario (in order of cost per patient).	Correct IPF diagnosis	Correct non IPF diagnosis	Negative effects and costs to be offset		Cases without agreement		Total cost	Cost per patient	Cost per correct diagnosis(TP+TN)	Average "QALY" gain per patient	Net benefit	Rank, according to net benefit.
			FN	FP	IPF	Non IPF						
Scenario 1	78	205	43	37			£174,194	£480	£615	0.0448	£151,280	2
Scenario 1 +MDT	106	187	14	55			£187,851	£518	£640	0.0495	£171,489	1
Scenario 2	78	209	43	33			£219,632	£605	£766	0.0464	£117,298	3
Scenario 2 + MDT	106	193	14	49			£364,904	£1,006	£1,218	0.0521	£13,049	4
Scenario 3	78	183	34	37	9	22	£469,090	£1,293	£1,795	0.0421	-£163,567	5
Scenario 3 + MDT	106	200	12	42	3	0	£669,170	£1,844	£2,184	0.0557	-£264,547	6
Scenario 4	78	168	7	37	36	37	£768,710	£2,118	£3,128	0.0444	-£446,193	7
Scenario 4 +MDT	106	195	6	42	9	5	£1,127,222	£3,106	£3,736	0.0560	-£721,037	8

Abbreviations: *FN = False negative; FP =False Positive; TP= True Positive; TN= True Negative*

Note: *Entries highlighted in strong green represent the most cost effective option. Entries highlighted in green show non-dominated options. Negative net benefit indicates that the strategy is not cost effective using a threshold of £20,000.*

Table 120: Sensitivity Analysis of varying time slots assigned per patient at local and specialist level MDT.

Scenario (in order of cost per patient).	Base case analysis with 8 minutes assigned per patient at local level MDT and 32 minutes assigned per patient at specialist level MDT			Sensitivity Analysis with 15 minutes assigned per patient at local MDT, 32 minutes at specialist level			Sensitivity Analysis with 15 minutes assigned per patient at specialist level MDT, 8 minutes at local level			Sensitivity Analysis with 15 minutes assigned per patient at local and specialist level MDT		
	Cost	NMB	Rank	Cost	NMB	Rank	Cost	NMB	Rank	Cost	NMB	Rank
Scenario 1	£480	£151,280	2	£480	£151,280	2	£480	£151,280	2	£480	£151,280	2
Scenario 1 +MDT	£518	£171,489	1	£548	£160,332	1	£518	£171,489	1	£548	£160,332	1
Scenario 2	£605	£117,298	3	£605	£117,298	3	£605	£117,298	3	£605	£117,298	3
Scenario 2 + MDT	£1,006	£13,049	4	£1,038	£1,366	4	£851	£69,101	4	£882	£57,944	4
Scenario 3	£1,293	-£163,567	5	£1,293	-£163,567	5	£1,293	-£163,567	5	£1,293	-£163,567	5
Scenario 3 + MDT	£1,844	-£264,547	6	£1,877	-£276,456	6	£1,623	-£184,379	6	£1,654	-£195,536	6
Scenario 4	£2,118	-£446,193	7	£2,118	-£446,193	7	£2,118	-£446,193	7	£2,118	-£446,193	7
Scenario 4 +MDT	£3,106	-£721,037	8	£3,141	-£733,732	8	£2,654	-£557,071	8	£2,685	-£568,228	8

Note: NMB = Net Monetary Benefit

Entries highlighted in strong green represent the most cost effective option. Entries highlighted in green show non-dominated options. Negative net benefit indicates that the strategy is not cost effective using a threshold of £20,000.

Table 121: Results of the sensitivity analyses where the QALY weighting associated with each outcome varied (cost per patient unchanged)

Scenario (in order of cost per patient).	Base case analysis			Sensitivity Analysis 1			Sensitivity Analysis 2			Sensitivity Analysis 3		
	Average "QALY" gain per patient	Net benefit	Rank, according to net benefit.	Average "QALY" gain per patient	Net benefit	Rank, according to net benefit.	Average "QALY" gain per patient	Net benefit	Rank, according to net benefit.	Average "QALY" gain per patient	Net benefit	Rank, according to net benefit.
Scenario 1	0.0448	£151,280	2	0.3924	£2,673,700	5	0.5462	£3,790,076	4	0.3957	£2,697,973	2
Scenario 1 +MDT	0.0495	£171,489	1	0.4332	£2,956,378	2	0.5666	£3,924,586	1	0.3612	£2,433,926	3
Scenario 2	0.0464	£117,298	3	0.4062	£2,728,505	4	0.5531	£3,794,759	3	0.4026	£2,702,656	1
Scenario 2 + MDT	0.0521	£13,049	4	0.4556	£2,974,878	1	0.5778	£3,861,654	2	0.3724	£2,370,993	4
Scenario 3	0.0421	-£163,567	5	0.3683	£2,204,230	7	0.5041	£3,189,730	7	0.3536	£2,097,627	6
Scenario 3 + MDT	0.0557	-£264,547	6	0.4878	£2,920,484	3	0.5911	£3,670,312	5	0.3857	£2,179,652	5
Scenario 4	0.0444	-£446,193	7	0.3888	£2,053,311	8	0.4740	£2,671,374	8	0.3235	£1,579,271	8
Scenario 4 +MDT	0.0560	-£721,037	8	0.4897	£2,526,532	6	0.5819	£3,195,945	6	0.3765	£1,705,285	7

Note: Entries highlighted in strong green represent the most cost effective option. Entries highlighted in light green show non-dominated options. Negative net benefit indicates that the strategy is not cost effective using a threshold of £20,000.

Table 122: Results of the sensitivity analyses where the diagnostic accuracy estimates where changed in line with different sources used in the clinical review (QALY associated with each diagnostic outcome as per the base case)

Scenario (in order of cost per patient).	Sensitivity Analysis 4 – Coutinho: HRCT			Sensitivity Analysis 5 - Peckham (HRCT)			Sensitivity Analysis 6 – Peckham (HRCT+ ATS)			Sensitivity Analysis 7 – Hunninghake (HRCT)			Sensitivity Analysis 8 – Thomeer & Slodkowska (HRCT+biopsy)			Sensitivity Analysis 9 – Flaherty &Slodkowska (biopsy)		
	Cost	QALY	Rank	Cost	QALY	Rank	Cost	QALY	Rank	Cost	QALY	Rank	Cost	QALY	Rank	Cost	QALY	Rank
Scenario 1	£480	0.052	1	£480	0.029	2	£480	0.038	2	£480	0.012	3	£480	0.067	1	£480	0.045	2
Scenario 1 +MDT	£518	0.050	2	£518	0.050	1	£518	0.050	1	£518	0.050	1	£518	0.050	3	£518	0.050	1
Scenario 2	£605	0.053	3	£605	0.032	4	£605	0.040	3	£605	0.015	4	£605	0.069	2	£605	0.046	3
Scenario 2 + MDT	£1,006	0.052	4	£1,006	0.052	3	£1,006	0.052	4	£1,006	0.052	2	£1,006	0.052	4	£1,006	0.052	4
Scenario 3	£1,279	0.046	5	£1,319	0.030	5	£1,305	0.036	5	£1,352	0.023	6	£1,276	0.054	5	£1,293	0.037	5
Scenario 3 + MDT	£1,844	0.056	6	£1,844	0.056	6	£1,844	0.056	6	£1,844	0.056	5	£1,844	0.056	6	£1,844	0.056	6
Scenario 4	£2,105	0.048	7	£2,144	0.036	7	£2,131	0.041	7	£2,177	0.031	7	£2,102	0.051	7	£2,118	0.031	7
Scenario 4 +MDT	£3,106	0.056	8	£3,106	0.056	8	£3,106	0.056	8	£3,106	0.056	8	£3,106	0.056	8	£3,106	0.056	8

Note: Costs and QALYs presented are mean per patient. Rank is based on calculated net monetary benefit (using a threshold of £20,000) with 1 representing the most optimal strategy. Options which are not dominated appear in light green. These options would improve in rank if the net monetary benefit was calculated with a higher threshold per QALY.

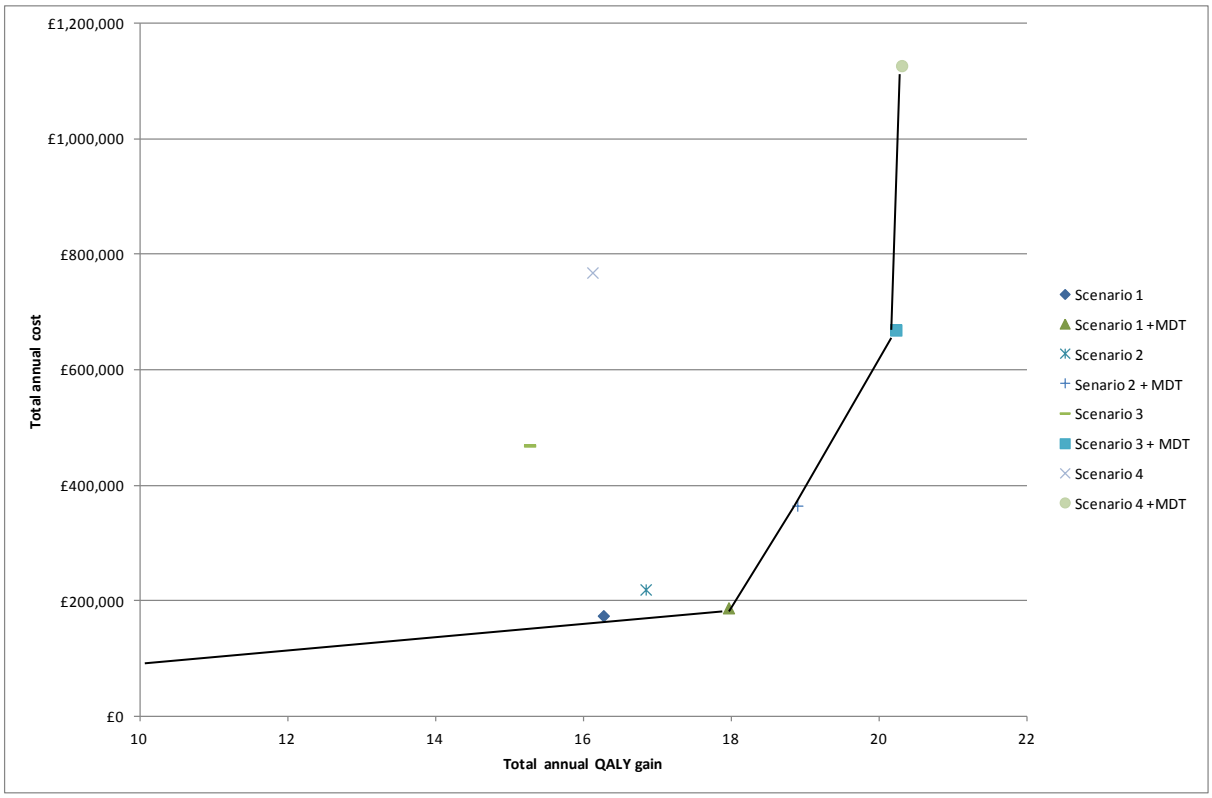
Table 123: Results of the sensitivity analyses where the diagnostic accuracy estimates are based on either community clinicians or academic clinicians.

Scenario (in order of cost per patient).	Correct IPF diagnosis	Correct non IPF diagno	Negative effects and costs to be offset	Cases without agreement	Total cost	Cost per patient	Cost per successful outcome	Average "QALY" gain per	Net	Rank, according to net

		sis	FN	FP	IPF	Non IPF			(TP+TN)	patient	Monetary Benefit	benefit.
Community Scenario 1	93	178	28	64	0	0	£174,194	£480	£644	0.039	£110,532	6
Academic Scenario 1	69	222	52	20	0	0	£174,194	£480	£598	0.048	£176,748	2
Community Scenario 1 +MDT	107	175	14	67	0	0	£187,851	£518	£666	0.044	£134,395	4
Academic Scenario 1 +MDT	106	225	15	17	0	0	£187,851	£518	£567	0.066	£291,598	1
Community Scenario 2	93	183	28	59	0	0	£219,632	£605	£796	0.042	£82,511	7
Academic Scenario 2	69	225	52	17	0	0	£219,632	£605	£748	0.049	£139,040	3
Academic Scenario 2 + MDT	106	228	15	14	0	0	£364,904	£1,006	£1,092	0.067	£123,413	5
Community Scenario 2 + MDT	107	181	14	61	0	0	£364,904	£1,006	£1,265	0.047	-£22,616	8
Academic Scenario 3	69	199	40	20	12	23	£464,150	£1,279	£1,733	0.046	-£131,934	9
Community Scenario 3	93	153	22	64	6	24	£476,993	£1,314	£1,939	0.035	-£221,853	11
Academic Scenario 3 + MDT	106	205	10	17	5	21	£651,726	£1,796	£2,097	0.063	-£197,025	10
Community Scenario 3 + MDT	107	190	14	52	1	0	£670,172	£1,847	£2,263	0.051	-£302,168	12
Academic Scenario 4	69	187	6	20	46	35	£763,770	£2,105	£2,987	0.051	-£395,865	13
Community Scenario 4	93	129	10	64	18	49	£776,613	£2,140	£3,508	0.032	-£540,985	14
Academic Scenario 4 +MDT	106	198	6	17	9	27	£1,109,777	£3,058	£3,653	0.062	-£659,705	15
Community Scenario 4 +MDT	107	190	5	47	9	6	£1,128,223	£3,109	£3,810	0.054	-£737,769	16

Note: Costs and QALYs presented are mean per patient. Rank is based on calculated net monetary benefit (using a threshold of £20,000) with 1 representing the most optimal strategy. Options which are not dominated appear in light green. These options would improve in rank if the net monetary benefit was calculated with a higher threshold per QALY.

Figure 115: Cost-effectiveness scatter plot for base case analysis



Appendix L: Cost-effectiveness analysis – Pulmonary rehabilitation for patients with Idiopathic Pulmonary Fibrosis

L.1 Introduction

Pulmonary rehabilitation aims to reduce disability in people with lung disease and to improve their quality of life while diminishing the health care burden. Provided by a multiprofessional team, pulmonary rehabilitation comprises of physical training, education, dietetics, occupational therapy, psychology, and social support. The benefits include improvements in exercise performance, health status, dyspnoea, and reduction in usage of health services. There can be involvement from the patient's family or carer. It assumes that optimal medical management has been achieved or continues alongside the programme, and thus rehabilitation should be seen as an adjunct rather than a comparator to other interventions [47].

Currently in the UK, pulmonary rehabilitation designed and provided specifically for the IPF population is not known to exist. Either patients are not offered pulmonary rehabilitation, or are offered places on pulmonary rehabilitation courses for patients with Chronic Obstructive Pulmonary Disease (COPD). Content in programmes designed for COPD may be inappropriate for an IPF population. Unlike COPD, a dry cough (which can become debilitating), shortness of breath, and fatigue are common symptoms of restrictive lung disease such as IPF and may not be addressed sufficiently in programmes designed for COPD patients. IPF patients do not need instruction on inhalers. Whilst COPD patients can have problems with high-flow supplemental oxygen, patients with restrictive lung diseases need as much oxygen as possible. Furthermore, pulmonary fibrosis progresses more rapidly than COPD, and the only "cure" currently available is a lung transplant. With a shorter median life expectancy on diagnosis, IPF patients need different consideration in pulmonary rehabilitation in managing expectations in end of life care and psychosocial support. As IPF is less common than COPD, patient members of the group expressed that a key benefit of a pulmonary rehabilitation programme provided for IPF patients could only be a reduction in the feeling of isolation in experiencing the condition, mitigating some of the associated anxiety and depression associated with IPF.

The reasons why pulmonary rehabilitation for IPF is lacking in the UK are complex, but may include medical indifference to non-pharmacological management, lack of scientific evidence, poor funding, and ineffective consumer demand. Clinical guidelines also appear to be lagging behind the strength of evidence in respect of rehabilitation [47]. No studies on the cost effectiveness of pulmonary rehabilitation in the IPF population were identified.

Pulmonary rehabilitation could be underutilised as a means of improving quality of life in people who live with IPF, including both patients and carers. Further, pulmonary rehabilitation programmes provided and designed specifically for IPF patients could prove to have additional benefit to programmes designed principally for COPD patients, although provision of IPF programmes would come at additional cost. It is suspected that rehabilitation could potentially prevent unnecessary contacts with the NHS as patients learnt how to self-manage symptoms of IPF, and therefore could reduce costs; however, there is currently an absence of evidence to demonstrate this. Overall the Guideline Development Group (GDG) considered a cost utility analysis to explore the cost effectiveness of offering IPF patients pulmonary rehabilitation in the current UK context to be a priority.

Pulmonary rehabilitation can be defined as a multi professional team led programme involving exercise, education and psychosocial support. The typical duration of one programme is 6-8 weeks, although some do run for longer. IPF patients could be defined as having category C rehabilitation needs, and therefore require a category 3a rehabilitation service. Having said this, the prevalence of IPF is lower than that of many other respiratory conditions for which pulmonary rehabilitation is offered. As such, we would expect only large district general hospitals or tertiary care centres to have a sufficiently large catchment area of referral to recruit the required number of patients to make use of economies of scale and make programmes offered exclusively to IPF patients viable in terms of cost effectiveness.

Patients with Category C rehabilitation needs:

- Patient goals are typically focused in restoration of function / independence and co-ordinated discharge planning with a view to continuing rehabilitation in the community.
- Patients require rehabilitation in the context of their specialist treatment as part of a specific diagnostic group (e.g. stroke).
- Patients may be medically unstable or require specialist medical investigation / procedures for the specific condition.
- Patients usually require less intensive rehabilitation intervention from 1-3 therapy disciplines in relatively short rehabilitation programmes (i.e. up to 6 weeks).
- Patients are treated by a local specialist team (i.e. Level 3a service) which may be led by consultants in specialties other than Rehabilitative Medicine (e.g. neurology / stroke medicine) and staffed by therapy and nursing teams with specialist expertise in the target condition.

Source: Cambridgeshire Joint Prescribing Group, 2010 [52]

Therefore, it is felt appropriate to explore all strategies in the context of a network of referral, allowing patients managed in smaller providers to be able to access the service provided. As IPF is relatively rare (we approximate 24 per 100,000 population [see Appendix J [349]]), IPF patients are usually under the outpatient care of a consultant in a large hospital and therefore we would expect any implementation cost of referral to be low given that a referral system should already be in place. To note, we would expect coordination of referral to sit comfortably within the context of the Multidisciplinary Team (MDT) (inclusive a full time coordinator and ILD nurse in each specialist hub); which is recommended and costed as part of the diagnostic pathway for IPF patients in this guideline.

The evidence base to inform the clinical course of IPF and the treatment effect in the health economic model is limited. The implications of a lack of available evidence to populate the model were considered, however, the developers felt a health economic model would still add value in determining thresholds and scenarios whereby certain strategies become more or less likely to be cost effective given that pulmonary rehabilitation is felt to be one of the few interventions that could benefit people with IPF.

L.2 Methods

L.2.1 Model overview

A cost-utility analysis was undertaken to evaluate the cost-effectiveness of a pulmonary rehabilitation course with IPF participants compared to a strategy of no offer of pulmonary rehabilitation. Lifetime quality-adjusted life years (QALYs) and costs were estimated from a current UK NHS and personal social services perspective. Both costs and QALYS were discounted at a rate of

3.5% per annum in line with NICE methodological guidance [348]. The cost effectiveness outcome of the model is cost per QALY gained.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- The GDG was consulted during the construction and interpretation of the model.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

L.2.1.1 Comparators

The below comparators were identified

1. No pulmonary rehabilitation
2. Community rehabilitation with exercise component
3. Pulmonary rehabilitation with exercise component and an educational component specifically designed for IPF patients.

Community rehabilitation is defined as a programme of exercise and physiotherapy only. It consists of bi-weekly attendance at pulmonary rehabilitation exercise session conducted weekly by community physiotherapist in local proximity to patients' residence. It is expected these sessions could be shared with other patient populations with respiratory conditions such as those with COPD, so long as safety of the patient in the case of over exertion was taken into account.

Pulmonary rehabilitation specifically designed for IPF patients is considered to be the exercise programme offered by community rehabilitation, with the addition of an educational component which would be delivered and overseen by a clinician (registrar or consultant level) with a specialist interest in IPF, alongside a ILD respiratory nurse, as well as one or more of the rehabilitation disciplines (physiotherapy, occupational therapy, psychology, dietetics, social work, vocational / educational support etc.).

L.2.1.2 Population

The base case considers a population of patients with a diagnosis of suspected or confirmed IPF. The analysis considers three subgroups of patients with IPF that have differential rates of disease progression. This is to allow for further analysis of the impact treatment effect duration on cost effectiveness. The proportion of patients in each subgroup is explored in a sensitivity analysis

L.2.1.3 Time horizon and cycle length.

The Markov model takes a lifetime horizon (maximum of 20 years post diagnosis) with a cycle length of 1 month to allow for changes in treatment effect duration.

L.2.1.4 Deviations from NICE reference case

The analysis will follow the standard assumptions of the reference case including discounting at 3.5% for costs and health effects, and incremental analysis is conducted. A sensitivity analysis using a discount rate of 1.5% for both costs and health benefit is conducted.

L.2.2 Approach to modelling

L.2.2.1 Model structure

The cost utility analysis uses a decision tree with Markov states which are based on a continuum of absolute Forced Vital Capacity Percentage (FVC %) predicted values ranging from 100% to 35%. A cohort of IPF patients with suspected or confirmed diagnosis of differing rates of disease progression is offered one of the compared strategies (in correspondence of the decision node of the tree) and then enters the Markov model which is depicted in Figure 116. It illustrates the health states in the model and possible transitions between them in each cycle. There is implicit time dependency within the model due to the increased risk of mortality as the cohort increases with age.

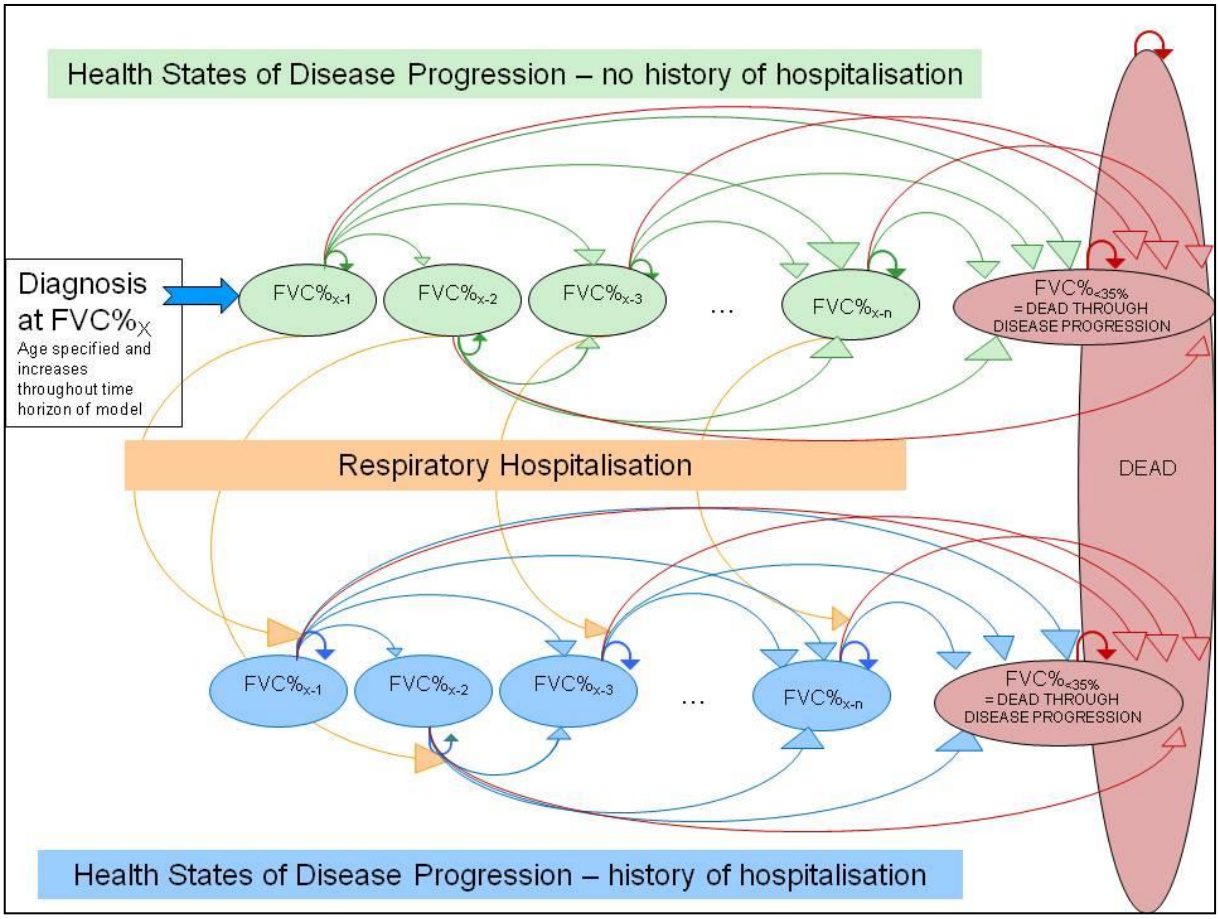
In a Markov model a set of mutually exclusive health states are defined that describe what can happen to the population of interest over time. People in the model can only exist in one of these health states at a time. Possible transitions are defined between each of the health states and the probability of each transition occurring within a defined period of time (a cycle) is assigned to each possible transition.

The health states are fixed according to categories of absolute FVC% predicted values. The cohort is subject to a probability of respiratory hospitalisation (which may include acute exacerbation), which acts as a transition event that moves the cohort to tunnel states that are also fixed on absolute FVC% predicted values. The tunnel states, however, have a higher associated probability of mortality due to the history of prior hospitalisation. The event of a respiratory hospitalisation occurs at the beginning of a cycle. Therefore from the first cycle, a patient may move to a health state with a lower FVC% predicted value without experiencing a hospitalisation, move to a lower FVC% predicted value having experienced hospitalisation or die. If a patient has a respiratory hospitalisation in the first month, for example, the probability of death in that cycle will take into account that the patient has experienced a hospitalisation. Additionally a half cycle correction is applied to all life years and costs accrued to reflect movement between states throughout the time of the cycle.

The rate at which the cohort progresses through the health states is determined by the probability of being in a subgroup experiencing a predefined rate of disease progression, as measured by a unit drop in FVC% predicted. The event of hospitalisation does not influence the rate of disease progression, and therefore the rate of disease progression for each subgroup is the same in pre and post hospitalisation states. This is due to a lack of data to parameterise this correlation. However, in line with evidence retrieved for the prognostic review, hospitalisation does influence probability of mortality and this has been captured in the model accordingly. To note, as a simplification to model disease progression, FVC% predicted can only deteriorate with time. In reality, some patients with IPF may experience an increase in FVC% predicted, however it is likely this is due to co morbidity such as emphysema or inaccuracies of the test. As there is no data to inform probability of mortality for this group of patients a sensitivity analysis was conducted where we assume this group experience mortality rates similar to patients with a slow, moderate or rapid rate of disease progression (please refer to 'Rate of disease progression' in section L.2.3.3 for further detail).

The rate of mortality is dependent on the age of the cohort, the absolute FVC% predicted value, the rate of disease progression and the history of hospitalisation [117]. Additionally it is assumed that the patient would not be in a state below 35% FVC% predicted as this is assumed to be unsustainable to life; therefore, movement beyond this is directed to the dead state. The intervention of pulmonary rehabilitation is only expected to influence QoL and a cost accrued within the model and does not influence any transition probability contained within the Markov model.

Figure 116: Simplified graphic of the Markov Model



Note: FVC%$_x$ denotes the starting lung function status of the cohort as measured by FVC% predicted. The diagram depicts a continuum of health states defined by FVC% predicted values. In the basecase, for example, the cohort starts in a health state of 75% FVC% predicted, and have a probability of moving to health states of 74% FVC% predicted, 73% FVC% predicted, 72% FVC% predicted and so on.

A one month cycle duration was used in this model to capture the potential decline in lung function and reflect disease progression. All the probabilities and on-going costs associated with community rehabilitation were converted to reflect the one month cycle length in the model. The model was run for repeated cycles, and the time spent in each health state was calculated. By attributing costs and quality of life weights to the time spent in each health state, total resource costs and QALYs can be calculated. There were no secondary outcomes recorded, however for clinical validation the median and mean life expectancy, alongside Kaplan Meier curves were produced for cohorts with differing starting characteristics. The model was run for 10,000 cycles in order to calculate costs and QALYs over a lifetime horizon.

To take into account the impact of disease progression on the ability to participate, it was assumed that pulmonary rehabilitation will not be of benefit when FVC% predicted is very low (approximately 45%) when patients would be unlikely to participate. To note, the patient's FVC% predicted value is used in this case as a proxy marker for the ability to participate for the purposes of modelling participation, and does not infer that an offer of rehabilitation should not be made for these patients as currently evidence does not exist to validate this assumption. A sensitivity analysis explores the scenarios whereby patients cannot participate in pulmonary rehabilitation within the cycle immediately post hospitalisation, and secondly whereby only a proportion of patients return to rehabilitation post any respiratory hospitalisation.

An assessment cost is applied at the beginning of each course of rehabilitation for every patient who is still alive in the model, regardless of the patient's assumed ability to participate due to prior

hospitalisation, low FVC% predicted value or otherwise. For the proportion of patients passing assessment and returning to rehabilitation, a cost for a place throughout the duration of the course is applied. The cost of pulmonary rehabilitation is not assumed to change in regard to the patient's clinical status or timing of the offer. As the probability of respiratory hospitalisation is the same in all compared strategies, the cost of the hospitalisation is not considered in the model.

A patient's quality of life is dependent on the time since the start of the model, treatment effect of the pulmonary rehabilitation course and the time period that has occurred since the beginning of the course. Quality of life is not adjusted according to FVC% predicted value. In case of death, the patient remains in the dead health state which is associated with no cost and a Health Related Quality of Life (HRQoL) equal to 0. In strategies where the cohort has had pulmonary rehabilitation an improved quality of life is added to the baseline quality of life.

The base case assumes that the maximum effect in quality of life recorded at follow up by the literature is only realised at the end of the programme (i.e. after 2 months) with a linear increase in quality of life until that point. This maximal benefit is sustained for a period of time after the programme finishes, and then declines to the point where the last long term follow up of quality of life was recorded by the literature (i.e. 6 months). From this point forth quality of life declines to baseline. Therefore, after the longest treatment effect duration has expired, the patient experiences the same quality of life as a patient at the same time period in the model that had not had the rehabilitation course.

For each strategy the expected healthcare resource costs and expected QALYs were calculated by estimating the costs and quality adjusted month for each state and then multiplying them by the proportion of patients who would be in that state (as determined by the differing transition probabilities associated with the strategy taken). Quality adjusted months were converted into quality adjusted life years.

The number of patients entering the Markov model for each subgroup was in accordance to the proportion the subgroup assumed in the population. In order to assess the cost-utility of implementing the compared strategies for a population, the resource costs and QALYs were summed for all subgroups in the cohort. The total costs and QALYs for a strategy were divided by the number of patients in the cohort, allowing an average cost and QALY per patient to be calculated. Comparing these results allows us to identify which strategy is the most cost-effective.

L.2.2.2 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 10,000 times for the base case and 2500 times for each sensitivity analysis – and results were summarised. The number of simulations used was chosen considering the Monte Carlo error of the incremental costs, QALYs and net monetary benefit using methods as described by Koehler et al[247]. It was set to ensure that the Monte Carlo error was not more than 5% of the standard error for each of these outcomes in all analyses, with the base case having an improved accuracy due to the greater number of simulations.

The way in which distributions are defined reflects the nature of the data, so for example utilities were given a beta distribution, which is bounded by zero and one, reflecting that a QoL weighting will not be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 124 and in the relevant input summary tables in section L.2.3. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 124: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Probability of being in a particular subgroup (i.e. having a certain rate of disease progression)	Dirichlet	Fitted to multinomial data. Represents a series of conditional distributions, bounded on 0-1 interval. Derived by the number of patients in the sample and the number of patients in a particular subgroup.
Mortality	Uniform	The risk calculator for mortality gave a range for a one year risk of mortality given four risk factors. A uniform distribution was taken to select from the range of the one year risk quoted for a given set of risk factors, before conversion to the appropriate probability for the cycle length.
Hospitalisation probability	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and Beta values were calculated as follows: Alpha=(number of patients hospitalised) Beta=(Number of patients)-(number of patients hospitalised)
Utility	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: $Alpha = mean^2 *(1-(mean/SE^2)-mean$ $Beta = Alpha *((1-mean)/mean)$

The following variables, were left deterministic (i.e. were not varied in the probabilistic analysis): cost-effectiveness threshold (which was deemed to be fixed by NICE), the resource, including time and cost of staff, required to implement each strategy (assumed to be fixed according to national pay scales and programme content) and the rate of disease progression (which was assumed to be linear).

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

L.2.3 Model inputs

L.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the reviews undertaken for the guideline, supplemented by additional data sources (including expert opinion) as required. In particular, estimates of treatment effect were derived from the only two RCTs identified by the systematic review conducted specifically for pulmonary rehabilitation, whereas other data sources were selectively chosen from the evidence retrieved as discussed in the following sections of this report. Model inputs were discussed and validated with clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in the table below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

1 **Table 125: Summary table of model inputs**

Input	Data	Source	Probability distribution
Comparators	• Pulmonary rehabilitation with educational component • Community rehabilitation • No rehabilitation	n/a	n/a
Population and subgroups	People diagnosed with IPF with a) rapid disease progression b) moderate disease progression c) slow disease progression	Expert opinion	n/a
Perspective	UK NHS & PSS	NICE reference case[348]	n/a
Time horizon	Lifetime	NICE reference case[348]	n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case[348]	n/a
Cohort settings			
Age on entry to model	70 years	Expert opinion	Fixed
FVC% predicted absolute value on entry to the model	75%	Expert opinion	Fixed
Mortality			
Mortality rate	Dependent on age, history of respiratory hospitalisation, baseline FVC% predicted value and 6 month change in FVC% predicted value.	Du Bois 2011 [117]	Uniform. Please see Table 124 for further explanation.
Quality of life (utility)			
Without rehabilitation	Time dependent , linear rate of decline between time points		
Year 0 Year 1 Year 2 Year 3 Year 4 Year 5 Year 6 Year 7 Year 8 onwards	0.892 0.852 0.821 0.769 0.720 0.677 0.607 0.569 0.488	Tzanakis, 2005 [482]	Beta
Community rehabilitation (exercise only)		Holland, 2008 [185]	
Absolute change at 3 months	0.068		Beta
Absolute change at 6 months	0.058		Beta
IPF rehabilitation (exercise with educational component)		Nishiyama, 2008 [355]	
Absolute change at 3 months	0.060		Beta
Absolute change at 6 months	0.060		Beta
Long term utility	Treatment effect diminishes at linear	Assumption	n/a

Input	Data	Source	Probability distribution
assumption	rate after 6 months to return to baseline at 7 months.		
Costs			
Rehabilitation costs per patient	Rehabilitation assessment: £96.13 Exercise only programme: £91.02 Education and exercise programme £117.06	Derived from resource use and unit costs below. [108,381]	n/a

L.2.3.2 Initial cohort settings

In the base case, the starting age and the extent of disease progression (as measured by absolute FVC% predicted) of the cohort in the model is estimated on the pooled mean reported for the baseline characteristics of the studies which inform the treatment effect. However, the study populations may not be reflective of one which is newly diagnosed in the UK context in that they may be older and have more extensive disease progression (i.e. a lower FVC% predicted). In a two way sensitivity analysis cohort settings are varied so that the impact an earlier and routine offer of pulmonary rehabilitation may be explored. For example, one of the analysis looks at an FVC% predicted of 100% and an age of 40 years old – a scenario which may be reflective of an offer of rehabilitation at an earlier stage of disease progression (with early diagnosis). Given that pulmonary rehabilitation would normally be prescribed on clinical judgement of symptoms such as "breathlessness" rather than on a clinical marker being reached, other scenarios explore the outcome if the initiation of pulmonary rehabilitation is at a lower absolute FVC% predicted value at which you would expect the patient to be experiencing symptoms such as breathlessness i.e. at 60%. Please refer to section L.2.5. for full details.

The cohort will enter the model with a prior probability of having a particular rate of disease progression. The proportion of the cohort experiencing a particular rate of disease progression is detailed below in section L.2.3.3

L.2.3.3 Baseline event rates (life expectancy and natural history)

The literature retrieved to inform the value of prognosis (Chapter 6) was reviewed to inform the parameters used to model that natural clinical course of the cohort. This information was supplemented by literature retrieved from a natural history search contained within the economic search (detailed in appendix D) and expert opinion.

Rate of Disease Progression

The natural clinical course of IPF is currently uncertain and unpredictable. Survival estimates for patients with confirmed/suspected IPF range from 1-10 years, with a median life expectancy of approximately 3 years. The literature and clinical experts in the GDG indicated that as understanding of the aetiology of IPF improves, it is likely further categorisation of the disease will occur allowing better definition of subgroups that follow a particular clinical course. Based on this information, the model allows for differentiation of rate of disease progression within the modelled IPF cohort and three subgroups are defined:

- IPF patients with **rapid disease progression** as indicated by a 6 month decline in **FVC% predicted of 10 or more units (%)**

- IPF patients with **moderate disease progression** as indicated by a 6 month decline in **FVC% predicted of 5 to 9 units (%)**
- IPF patients with **slow disease progression** as indicated by a 6 month decline in **FVC% predicted of less than 5 units (%)**

The probability of moving between health states of an absolute FVC% predicted value was calculated for each subgroup according to the rate of FVC% predicted decline specified above. To do this, it was assumed that at 6 months the subgroup would have equal chance of experiencing an absolute unit change within the range specified. The unit decline per month and subsequently per cycle was calculated, assuming that decline was linear and rounding the unit decline per cycle to the nearest one percent of FVC% predicted (as the health states are defined per percent). Due to the rounding to the nearest percent, the model applies the below in the deterministic analysis:

- All IPF patients with **rapid disease progression** experience a decline of 2% per month leading to a 6 month decline in FVC% predicted of 12 units (%)
- IPF patients with **moderate disease progression** have an 80% chance of experiencing a decline of 1% per month leading to a 6 month decline in FVC% predicted of 6 units (%) and 20% chance of experiencing a decline of 2 units change per month leading to a 6 month decline in FVC% predicted of 12 units (%). Across the subgroup, a mean decline of 1.2 units is applied per month, or a 7.2 unit decline per 6 months
- IPF patients with **stable disease progression** have a 60% chance of experiencing a decline of 0% per month leading to a 6 month decline in FVC% predicted of 0 units (%) and 40% chance of experiencing a decline of 1 unit change per month leading to a 6 month decline in FVC% predicted of 6 units (%).Across the subgroup, a mean decline of 0.6 units is applied per month, or a 3.6 unit decline per 6 months.

In the probabilistic analysis, rounding error is accounted for so that the mean unit decline experienced in each subgroup is exactly the midpoint of the range over a large number of simulations.

It is recognised that the above subgroups are not inclusive of all IPF patients, as some patient's FVC% predicted may improve post diagnosis. This improvement may in part be explained by co-morbidities such as emphysema, or by variation or discrepancy in pulmonary function testing. However, no evidence was retrieved to inform the duration of improvement in FVC in IPF patients or the impact this improvement would have on future rate of disease progression, hospitalisation or mortality. On the premise that other factors (such as co morbidity) could mask IPF disease progression (when measured by a change in FVC% predicted), it was agreed reasonable to assume patients with improved IPF would incur the same or more risk of mortality as patients with slow disease progression.

The proportion of the cohort entering the model with a particular rate of disease progression was estimated by averaging the proportion of patients with each rate of disease progression observed in the BUILD1 trial[464] and UK unpublished hospital data provided by a clinical member of the GDG (Table 126). The calculation of the proportion of patients in each subgroup in the base case excluded data retrieved from patients whom FVC% predicted improved. In a sensitivity analysis, the proportion of patients in each subgroup was explored, firstly by assuming patients who had an improved FVC% predicted had the same mortality risk as those with slow disease progression and secondly by assuming a patients mortality risk was influenced by the rate of change (improvement or decline) in FVC% predicted, with those experiencing a small improvement experiencing the same mortality risk as those with a small decline, and patients with moderate improvement experiencing the same mortality risk as those with moderate decline(SA1 and SA2 respectively in the table below).

Table 126: The proportion of patients experiencing a given rate of disease progression according to FVC% predicted (per unit of %)

Disease progression within 6 months (defined by FVC% predicted unit change)	Swigris (2010) [a]	UK data source [b]	Base case estimate [c]	SA1 [d]	SA2 [e]	SA3	SA4	SA5
Moderate improvement	6% (n=8)	13% (n=24)						
Small improvement	8% (n=10)	24% (n=45)						
Slow disease progression	53% (n=68)	33% (n=60)	57% (n=128)	69% (n=215)	58% (n=183)	100%		
Moderate disease progression	20% (n=26)	15% (n=28)	24% (n=54)	17% (n=54)	27% (n=86)		100%	
Rapid disease progression	13% (n=17)	15% (n=27)	19% (n=44)	14% (n=44)	14% (n=44)			100%

(a) Swigris et al(2010) categorisation of disease progression in absolute change of FVC% predicted: Moderate improvement = >+12%; Small improvement=+7% to +12%; Slow disease progression=-7% to+7%; Moderate disease progression = -12% to -7% ; Rapid disease progression=>-12%

(b) The UK data source categorisation of disease progression in absolute change of FVC% predicted: Moderate improvement =>+5%; Small improvement=0% to 5%; Slow disease progression=0% to -5%; Moderate disease progression =-5% to -10%; Rapid disease progression=>-10%

(c) Base case categorisation of disease progression: Slow disease progression=0 to 5 unit decrease; Moderate disease progression =5 to 10 unit decrease; Rapid disease progression=>10 unit decrease. Proportions are an average of data sources, excluding with patients with improved FVC% predicted.

(d) Assumption that all patients with improved FVC experience same mortality risk as those with slow disease progression.

(e) Assumption that only patients with small improvement in FVC experience the same mortality risk as those with slow disease progression, and the remainder experience the same mortality risk as those with moderate disease progression.

Rate of Respiratory Hospitalisation (including acute exacerbation)

Findings from Du Bois et al (2011) [117] indicate that previous hospitalisation for a respiratory cause is a prognostic risk factor for mortality. Further, hospitalisation was indicated as a potential event that would prevent participation in a programme. A natural history search retrieved three papers which potentially could inform the rate of hospitalisation from respiratory causes in the IPF population, taking into account disease progression as measured by FVC% predicted.

Kondoh et al (2010)[248] found a 10% decline in FVC% predicted at 6 months found to be independent risk factor of AE, reporting a hazard ratio of 2.60 (95% CI 1.01-7.45). Additionally these authors found that acute exacerbation, when adjusted for FVC% predicted and decline in FVC % predicted, was an independent predictor of survival (with a hazard ration of 2.79 [95% CI 1.59-4.88]). In a multivariate analysis, Song et al. (2011) [445] reported a hazard ratio of 0.979 (0.964-0.995) for "low" FVC% predicted values. Whilst both papers were informative, neither papers specified the comparator used in the calculation of the hazard ratio, making the use of their data unviable in the model.

Martinez et al. (2005) [304] reported that 38 of 168 patients had respiratory hospitalization. The authors report that 82 patients had an FVC % predicted value of less than 63%, and 25 of these patients had a respiratory hospitalisation within 18 months of follow up. 86 patients had an FVC % predicted value of over 62%, 13 of whom had a respiratory hospitalisation in the same time. Using this data, the following probability of hospitalisation in the model was derived.

Table 127: Probability of respiratory hospitalisation according to FVC% predicted value. Source: Martinez et al. (2005).

	N	Number of hospitalisations (over 18 month period)	Probability of 1st hospitalisation (over 18 month period)	alpha	Beta	Rate	Probability of hospitalisation over a one month cycle
Complete cohort	168	38	0.23	38	130	0.0142	0.01
FVC% predicted <=62% (n=82)	82	25	0.30	25	57	0.0202	0.02
FVC% predicted >62% (n=86)	86	13	0.15	13	73	0.0091	0.009

Rate of Mortality

Du Bois et al (2011) [117] provide a mortality risk scoring system taking into account 4 risk factors (age, history of hospitalisation, FVC% predicted and 24 week change in FVC% predicted) providing baseline risk data of mortality. The hazard ratio derived by multiple regression and score assigned to each risk factor is given in Table 128, and the risk of 1 year mortality by composite score is given in Table 129.

Table 128: Multivariate analysis of predictors of all-cause mortality among patients with idiopathic pulmonary fibrosis

Heading	HR	LCI	UCI	Score
Age				
>=70	2.21	1.35	3.62	8
60-69	1.49	0.90	2.46	4
<60	1			0
History of respiratory hospitalisation				
yes	4.11	2.57	6.58	14
no	1			0
FVC% predicted				
<=50	5.79	2.55	13.15	18
51-65	3.54	1.95	6.44	13
66-79	2.2	1.19	4.09	8
>=80	1			0
24 week change in FVC% predicted				
<=-10	7.99	5.26	12.14	21
-5 to-9.9	2.60	1.75	3.85	10
>-5	1			0

Table 129: Expected 1-year probability of death corresponding to total risk score shown in Table 128

Total Risk score	Expected 1 year Risk of death
0-4	<2%

Total Risk score	Expected 1 year Risk of death
8-14	2-5%
16-21	5-10%
22-29	10-20%
30-33	20-30%
34-37	30-40%
38-40	40-50%
41-43	50-60%
44-45	60-70%
47-49	70-80%
>50	>80%

The model uses the one year risk of mortality calculator detailed in Table 129 to estimate the probability of mortality in each cycle of each health state. This was done by determining the score each subgroup would have at any particular time point in the model by taking into account increasing age as the cohort progressed through the model, whether the event of hospitalisation had occurred through use of tunnel states and a decreasing absolute FVC % predicted as the FVC% declined in accordance to which subgroup they were in. For simplicity as the model cycle was 1 month in duration, we assume that a 6 month decline in FVC% predicted is interchangeable and equivalent to the 24 week decline in FVC% predicted specified by the Du Bois study. The probability of mortality in one cycle was calculated from the one year risk using methods outlined in section L.2.4

The nature of the Markov model, the use of the Du Bois data and the model structure imposes several assumptions regarding the natural history of the IPF patients:

- The rate of disease progression is linear and we can divide into subgroups accordingly. If the rate of disease progression increases with time, the model may underestimate the mortality risk in later cycles of the model.
- The risk of hospitalisation is only influenced by absolute FVC% predicted values, and not by rate of disease progression (as there is an absence of evidence to suggest this). If hospitalisation increases with an increased rate of disease progression, the model may underestimate mortality risk.
- Due to computational complexity, the model only has the capacity to have memory of one previous hospitalisation, which may have occurred at any point since entry of the cohort. Using the hazard ratios specified by Du Bois et al (2011) [117] could result in overestimation of mortality risk in cycles post 24 weeks. However, this overestimation may be mitigated by the fact that 25% of patients with history of hospitalisation will be expected to have multiple episodes [445].
- The model assumes that previous hospitalisation only affects the risk of mortality, it does not decrease FVC % predicted value or increase rate of disease progression. If hospitalisation does result in a rapid drop in FVC% predicted value, the model may underestimate mortality risk post hospitalisation and overestimate life expectancy, as a lower proportion of the cohort surviving a hospitalisation will reach an FVC% predicted value of <35% (the dead through disease progression state) in the time period expected.

The assumptions outlined above were discussed in light of findings from the prognostic clinical review. In order to clinically validate the model output, the median life expectancy and disease trajectory of cohorts with differing baseline characteristics was produced. The median life expectancies mean life years gained per patient and Kaplan Meier curves are given for cohorts of differing age and FVC% predicted at baseline in Appendix M: M.

L.2.3.4 Quality of Life (Utilities)

The Quality Adjusted Life Year (QALY) is a measure of a person's length of life weighted by a valuation of their Health Related Quality of Life (HRQoL) over that period. Utilities are a measurement of the preference for a particular health state, with a score ranging from 0 (death) to 1 (perfect health). To inform the utility of the time spent in the model; a search of the economic and quality of life literature identified utilities which have been used in previous economic evaluations regarding idiopathic pulmonary fibrosis.

A number of instruments are used in assessing the HRQoL associated with interventions in IPF. Two commonly instruments are the generic SF36 and the disease specific SRGQ questionnaires.

The SF36 has been validated in the IPF population [305,464] and can be mapped to EQ5D using the methods cited by Ara and Brazier [[20] equation 1]. The use of SRGQ (St Georges Respiratory Questionnaire) has also been suggested as a valid tool to assess quality of life in the IPF population [464,482,510] and can also be mapped to the EQ5D by the algorithm developed by Starkie and colleagues[447]. Where estimates of utility either directly from EQ5D estimates or from values mapped from SF36 are not obtainable, consideration will be given to mapping SRGQ scores to the EQ5D.

Uncertainty associated with any reported scores can also be taken into account in the mapped EQ5D estimate by using probabilistic methods and simulation. The mapped EQ5D estimate, with confidence interval, is a composite score that will allow an assessment of the change in quality of life provided by an intervention. For full details of the method and calculations used in mapping to the EQ5D, please refer to section L.2.4. When assessing the evidence, the limitations of both the HRQoL instruments and mapping methods were taken into consideration, and these are outlined in section 0

Estimating quality of life throughout the natural clinical course of IPF (baseline QoL)

The quality of life search and the history search retrieved two studies [464] [482] that provided potential means of estimating the quality of life throughout the natural clinical course of IPF. The two data sources lend themselves to two different approaches to estimating the baseline QoL of patients in the no rehabilitation strategy of the model.

Estimating baseline utility – approach 1:

Swigris et al. (2010) [464] used data from the BUILD-1 trial in a retrospective analysis to determine a minimally important difference in QoL of IPF patients as measured by the SF36 and SRGQ. The authors used distributional and anchor based methods, and report regression equations for each SF36 domain for a unit change in FVC% predicted. These are shown alongside the expected decline in the value of the SF36 domain for a unit decline in FVC% predicted in Table 130. The final row gives the decline in utility you would expect with the associated decline in FVC% predicted if these values were mapped to the EQ5D.

Table 130: Regression equation for a change in SF36 domain and FVC% predicted. Source: Swigris et al (2010)/

SF36 domain	Regression equation	Decline in SF36 domain score that corresponds to a raw change in FVC% predicted of:		
		5%	10%	15%
Physical Functioning (PF)	$\Delta PF = 0.7 + 0.18(\Delta FVC)$	1.6	2.5 (1.1-3.9)	3.4
Physical Role (RP)	$\Delta RP = 1.7 + 0.16(\Delta FVC)$	2.5	3.3 (1.3 – 5.4)	4.1
Bodily Pain (BP)	$\Delta BP = -0.2 + 0.14(\Delta FVC)$	0.5	1.2 (0.5 – 3.0)	1.9
General Health (GH)	$\Delta GH = -0.02 + 0.07(\Delta FVC)$	0.33	0.7 (-0.5-1.8)	1.03

SF36 domain	Regression equation	Decline in SF36 domain score that corresponds to a raw change in FVC% predicted of:		
		5%	10%	15%
Vitality (VT)	$\Delta VT = 0.47 + 0.16(\Delta FVC)$	1.27	2.1 (0.8 – 3.4)	2.87
Social Functioning (SF)	$\Delta SF = 1.3 + 0.37(\Delta FVC)$	3.15	5.0 (2.1- 7.0)	6.85
Emotional Role (RE)	$\Delta RE = 1.0 + 0.27(\Delta FVC)$	2.35	3.7 (1.4-6.1)	5.05
Mental Health (MH)	$\Delta MH = 0.96 + 0.04(\Delta FVC)$	1.16	1.3 (0.8 – 2.8)	1.56
Estimated decline in utility (as mapped by to the EQ5D)		0.0457116	0.0534191	0.0611266

(a) The study used data recorded at baseline and 6 months. Note that the range was only reported for a decline of 10% in FVC% predicted value.

Table 131 shows the expected FVC% predicted value at given time points in the model for the different subgroups, such that it gives the predicted utility of a patient at a given time point in the model if the utility decrements specified for a given decline in FVC% predicted (of that subgroup) were used. It was decided that it would become to0 computationally burdensome to find the utility decrement associated with each FVC% predicted unit change within the model, given the number of health states and tunnel health states required to represent a continuum and all 8 SF36 domains would need to be taken into account before mapping to the EQ5D. Further, although application of a different baseline utility may influence the accuracy of total QALY gain, as the treatment effect is added to the baseline in the model, assumptions regarding baseline utility would not impact greatly on the incremental effect calculated.

Table 131: Predicted QoL according to decline in FVC% predicted per year

Time (years)	Slow decline (2.5% every 6 months)		Moderate decline (7.5% every 6 months)		Fast decline (12.5% every 6 months)	
	FVC% predicted	QoL estimate	FVC% predicted	QoL estimate	FVC% predicted	QoL estimate
0	100%	1.00	100%	1	100%	1
1	95%	0.92	85%	0.90	0.75	0.89
2	90%	0.83	69%	0.80	0.5	0.77
3	85%	0.75	52%	0.70	0.25	0.66
4	80%	0.67	34%	0.60		
5	75%	0.58				
6	70%	0.50				
7	65%	0.41				
8	60%	0.33				

Estimating baseline utility – approach 2:

Tzanakis et al (2005) [482] reports on a cross sectional study examining the correlation between quality of life measures and pulmonary function tests. The authors found that duration of disease was significantly correlated with SGRQ scores (r=0.483, p=0.01). Using the methodology outlined in section L.2.3.4, utilities for each year post diagnosis are given in Table 132.

Table 132: Quality of Life of IPF patients over an 8 year time horizon. Source: Tzanakis et al. (2005).

Time (years)	SRGQ score	EQ5D Utility Estimates (mapped from SRGQ)

Time (years)	SRGQ score	EQ5D Utility Estimates (mapped from SRGQ)			
		Estimate	SEM	LCI	UCI
0	24	0.89	0.02	0.84	0.93
1	30	0.85	0.03	0.79	0.90
2	34	0.82	0.03	0.75	0.87
3	40	0.77	0.04	0.70	0.83
4	45	0.72	0.04	0.64	0.79
5	49	0.68	0.04	0.59	0.75
6	55	0.61	0.05	0.51	0.69
7	58	0.57	0.05	0.47	0.66
8	64	0.49	0.05	0.38	0.59

Note: Sample size (n) = 25; Male = 84%; Age = 66±11(sd); FVC% pred = 68.8±16 (sd). Rate of FVC% pred. decline = NR; No participating subjects had any significant medical history or co morbidity. 32% had supplemental oxygen use. SGRQ = 37.7 ± 18.9(sd). SRGQ standard error approximated at 3.78 = (18.9/√25). Please note that SRGQ scores were read from graph as exact values were not provided on request.

In the model, each life year in the no rehabilitation strategy is weighted with the respective utility detailed in Table 132. It was not possible to estimate from the paper the quality of life beyond the 8th year, it was assumed that the quality of life for patients living beyond 8 years was the same as that derived for the 8th year of the model. The model assumes that baseline quality of life is not influenced by the patient's FVC% predicted, hospitalisation or rate of disease progression. If quality of life does decline with these factors, the model is likely to overestimate the total QALY gain of the subgroups with moderate and rapid decline across all strategies. To take this limitation into account, and to avoid error in estimating the incremental QALY gain between those receiving pulmonary rehabilitation and those without, the model adds a mean difference of effect found by the clinical review, rather than applying a relative treatment effect (i.e. QoL improves by 25%).

L.2.3.5 Treatment effect

The clinical review identified two RCTs [185 355] and 6 cohort studies [213,253,373,404,465] to inform the treatment effect of pulmonary rehabilitation for an IPF and ILD population. A further study that looked at only psychosocial support specifically[285]. Three of the cohort studies that gave SF36 values at baseline and post intervention[213,253,373]. Due to the quality of these observational studies, it was decided that only the programmes specified by the RCTs should be used to inform the model.

One RCT[185] suggested there may be a small improvement in 6 month survival following an exercise programme, however there was too much uncertainty to determine whether there was a difference in this parameter. As such, it is not expected that pulmonary rehabilitation will delay disease progression; rather that it improves the quality of life throughout the first stages of disease progression. Therefore the only treatment effect examined in the model is the quality of life improvement found with pulmonary rehabilitation. Pulmonary rehabilitation does not influence the probability of disease progression, respiratory hospitalisation (including acute exacerbation) or death. This means that the life expectancy and the number of hospitalisations will be the same across compared strategies. For this reason the number and cost of healthcare contacts is not recorded by the model.

The two RCTs [355 185] suggested that pulmonary rehabilitation improved quality of life.

Nishiyama et al (2008) [355] showed that quality of life, as measured by the St Georges Respiratory questionnaire, improved moderately by a nine week programme that had some educational elements (not specified). Table 133 gives the St Georges Respiratory Questionnaire scores presented by Nishiyama et al. 2008, and Table 134 shows the utility estimates used in the model when these

scores were mapped to the EQ5D using the methods stated in section L.2.4.1. An absolute effect difference in utility of 0.060 was found at the end of the pulmonary rehabilitation programme between the control and intervention arm.

Table 133: St Georges Respiratory Questionnaire Scores presented by Nishiyama et al (2008)

SGRQ Domain	Control (n=15)				Rehab (n=13)				Difference between groups in change from baseline
	Baseline	SD	Post intervention	SD	Baseline	SD	Post intervention	SD	
Symptoms	38.0	25.8	40.6	21.2	53.4	25.8	56.4	22.3	-5.7
Activity	50.4	26.2	54.0	22.6	62.5	16.9	64.7	17.1	-5.8
Impacts	29.9	23.7	32.9	23.5	36.5	17.5	39.7	17.6	-6.2
Total	37.8	22.7	40.9	20.7	47.3	17.4	50.2	16.3	-6.1

Note: SD = Standard deviation

Table 134: Utility estimates used in the model, as derived by mapping the SGRQ scores to the EQ5D

	Total SGRQ	Mapped to the EQ5D from SGRQ	SE of SGRQ	α	β
Control - baseline	37.800	0.786	5.861	40.314	66.337
Rehab - baseline	50.200	0.661	4.826	49.297	48.904
Control - post	40.900	0.757	5.345	44.857	64.817
Rehab - post	47.300	0.693	13.923	46.313	51.601
Difference - control	3.100	-0.028			
Difference - rehab	-2.900	0.032			
Absolute mean difference		0.060			

Note: Percentage male = not reported, therefore assumed at 70%; SE = Standard error calculated by dividing standard deviation by the square root of the sample size. Alpha and Beta calculated using standard error. A beta distribution was used in the probabilistic sensitivity analysis.

Holland et al (2008) showed that quality of life as measured by the SF36 improved to a similar extent to that found by Nishiyama et al. (2008). Table 135 gives the mean SF36 scores (provided as summary data from the authors), with the mapped values as calculated in the methodology stated in section L.2.4. The data shows that at three months follow up, an absolute effect difference in utility of 0.068 was found between the control and intervention arm, and at six months follow up the absolute difference in effect had decreased to 0.058. Table 136 gives the uncertainty estimates used in the probabilistic sensitivity analysis for this parameter.

Table 135: Treatment effect of exercise programme as detailed by Holland et al (2008) [185]

			Mean SF36 Dimension Score								Utility (Mappe
	Sam	Time	PH	RP	BP	GH	SF	RE	MH	V	

	ple size	point									d EQ5D from SF36)
Control	27	Base	17.85	5.11	7.78	14.10	7.26	4.67	21.37	13.15	0.18
	27	3 months	17.11	5.00	7.50	12.68	7.15	4.74	20.67	12.11	0.18
	27	6 months	16.11	4.81	7.51	12.26	6.26	4.56	20.22	11.81	0.17
Rehab	28	Base	18.00	4.78	7.70	13.59	7.00	4.67	22.59	12.19	0.19
	28	3 months	19.41	4.96	8.10	14.16	7.92	5.00	24.26	14.70	0.20
	28	6 months	17.78	4.64	7.95	13.90	6.79	4.71	22.39	13.07	0.18

Table 136: Uncertainty estimates for the SF36 values provided by Holland for use in the probabilistic sensitivity analysis

Arm of trail	t [a]	Standard Error for each SF36 domain								Alpha and Beta values derived by method of moments (Briggs)															
										PH		RP		BP		GH		SF		RE		MH		V	
		PH	RP	BP	GH	SF	RE	MH	V	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β
Control	0	4.49	6.58	5.34	3.93	5.40	9.07	4.00	3.67	46	71	13	33	49	36	73	87	50	26	16	13	92	49	84	100
	3	4.07	7.06	5.92	4.02	4.96	7.90	4.20	4.19	51	88	9	27	38	32	60	88	60	29	23	14	83	49	58	80
	6	4.07	5.82	6.53	4.31	5.64	8.10	3.85	3.74	40	88	10	37	31	26	48	78	44	30	22	13	98	61	72	101
Rehab	0	4.24	5.46	4.39	3.41	5.55	8.01	3.12	3.29	53	79	10	42	74	50	88	121	47	26	21	17	151	68	89	132
	3	4.47	7.47	5.20	3.02	5.48	8.68	3.08	3.36	56	67	8	24	53	33	114	154	48	20	19	12	143	43	115	105
	6	4.47	6.32	5.52	4.41	5.40	8.95	3.34	4.37	46	72	5	26	48	28	54	71	48	34	15	15	129	48	59	70

Note: Standard error calculated by dividing the standard deviation by square root of the sample size. T= time since programme start (months). Alpha and Beta values derived by method of moments[46] . A beta distribution was used in the probabilistic sensitivity analysis.

Treatment effect duration

No evidence was retrieved to inform treatment effect duration or the impact of pulmonary rehabilitation maintenance. The base case takes the conservative assumption that utility increases at a linear rate from baseline to the maximum absolute difference seen by the RCT at the end of the pulmonary rehabilitation course (2 months). At this point the maximum absolute difference in utility is sustained until the midpoint follow-up period of 3 months specified by Holland et al. (2008) has surpassed. From this midpoint the utility difference between those who do not have rehabilitation and those who have had rehabilitation declines at a linear rate until the observed difference in utility at the long term follow up time point at 6 months is achieved. In the base case, it is assumed no further treatment effect will be observed past this time period, and the rehabilitation cohort then experiences the same utility as the cohort that did not have rehabilitation. In a sensitivity analysis, a long term treatment effect diminishing at a linear rate is tested, with treatment effect completely disappearing after 6 months (base case), 9 months, 12 months, 15 months, 18 months and 24 months.

Treatment effect of repeated programmes

There was no evidence to inform whether patients undergoing a repeated programme would experience the same increase in quality of life as they had experienced with the first programme. A sensitivity analysis was conducted whereby the treatment effect was reduced by a given percentage compared to that experienced by completing a previous programme by applying a treatment effect multiplier powered to the number of programmes previously undertaken. So for example, a patient on their second programme of rehabilitation will only experience 80% of the quality of life improvement that they had experienced on the first programme. A patient on their third programme would experience 80% of the quality of life improvement they had experienced on their second programme and so on.

A three-way deterministic sensitivity analysis explores the impact of differing treatment effect assumptions as outlined in section L.2.5 to aid decision making regarding the viability of offering pulmonary rehabilitation more than once. The graphs below illustrate the utility applied for the programmes given a 12 month long term treatment effect with an offer of rehabilitation every 12 months and every 9 months. Figure 117 and Figure 118 illustrate this with the treatment effect multiplier set to 100% so no difference in effect was observed between repeated programmes, and Figure 119 and Figure 120 show the same over a longer time horizon, with the treatment effect multiplier set to 80% which shows the decline in effect with each repeated programme.

In some cases, where the long-term treatment effect was long and the magnitude of treatment effect with each repeated offer decreased substantially, it was possible that at the time point of the repeated programme the utility arising from sustained effect of the first programme was higher than that produced by the second programme. The model was programmed to ensure that in such instances the sustained treatment effect was applied appropriately by modelling the utility gain in each repeated course (according to magnitude of effect and treatment effect duration) and selecting the highest utility possible in each cycle.

Figure 117: Utility estimates applied in the first 24 months of the model, whereby the pulmonary rehabilitation course was repeated at 12 months, and long term treatment effect duration of 12 months was applied.

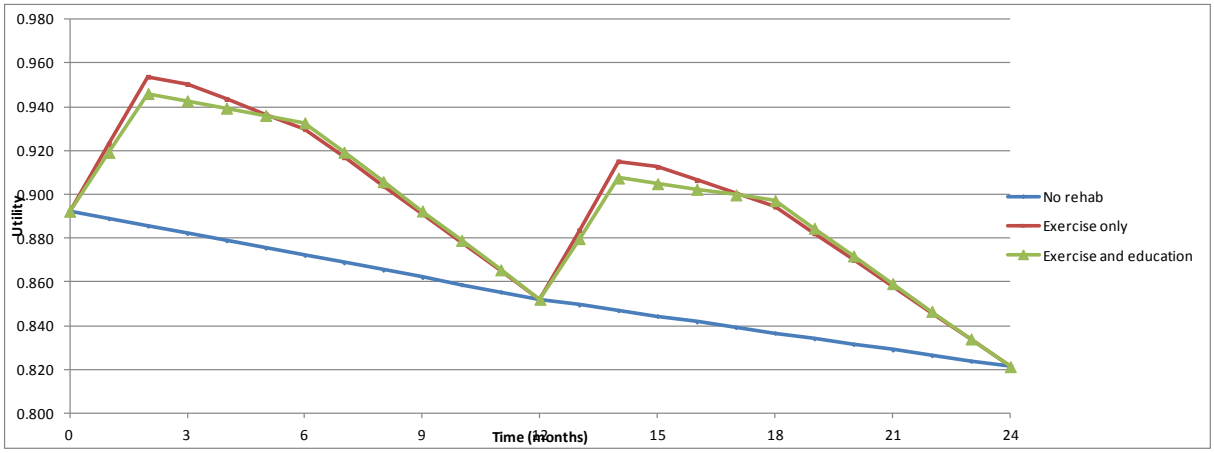


Figure 118: Utility estimates applied in the first 24 months of the model, whereby the pulmonary rehabilitation course was repeated at 9 months, and long term treatment effect duration of 12 months was applied.

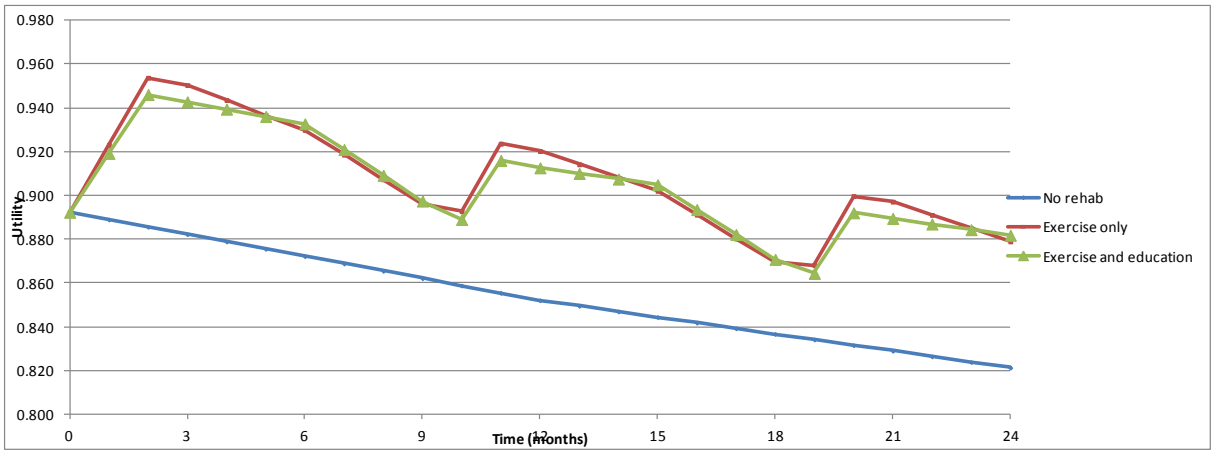


Figure 119: Utility estimates applied in the first 60 months of the model, whereby the pulmonary rehabilitation course was repeated at 12 months, and long term treatment effect duration of 12 months was applied. Each subsequent programme is 80% as effective as the previous programme experienced before.

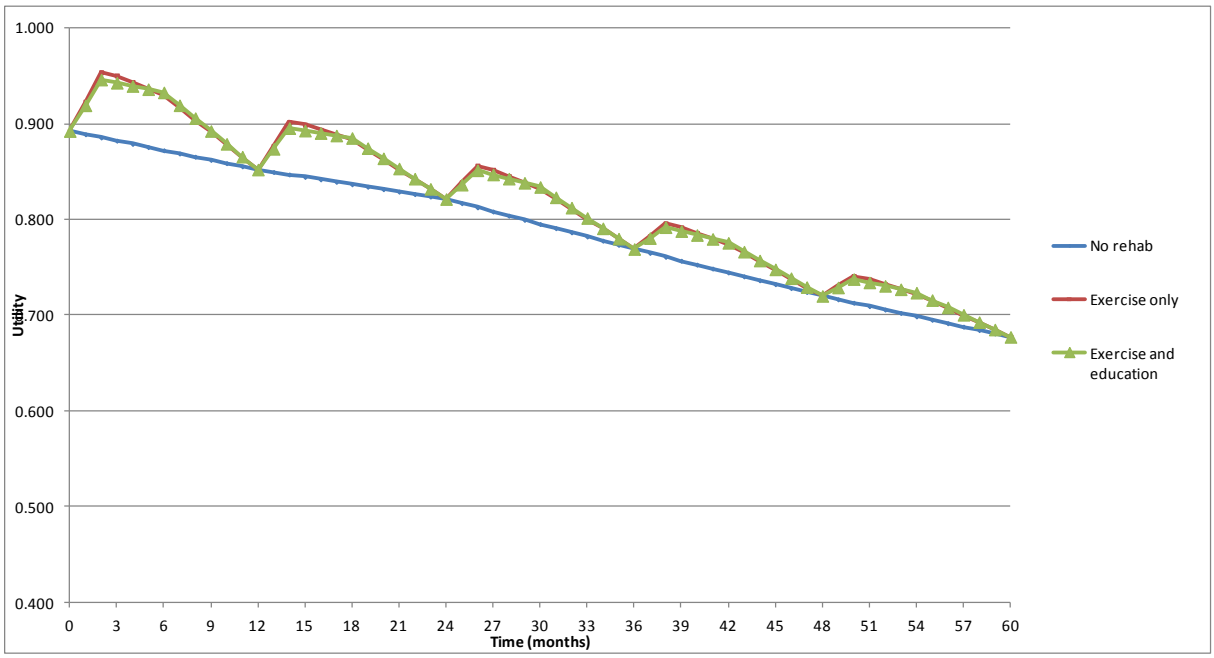


Figure 120: Utility estimates applied in the first 60 months of the model, whereby the pulmonary rehabilitation course was repeated at 9 months, and long term treatment effect duration of 12 months was applied. Each subsequent programme is 80% as effective as the previous programme experienced before.

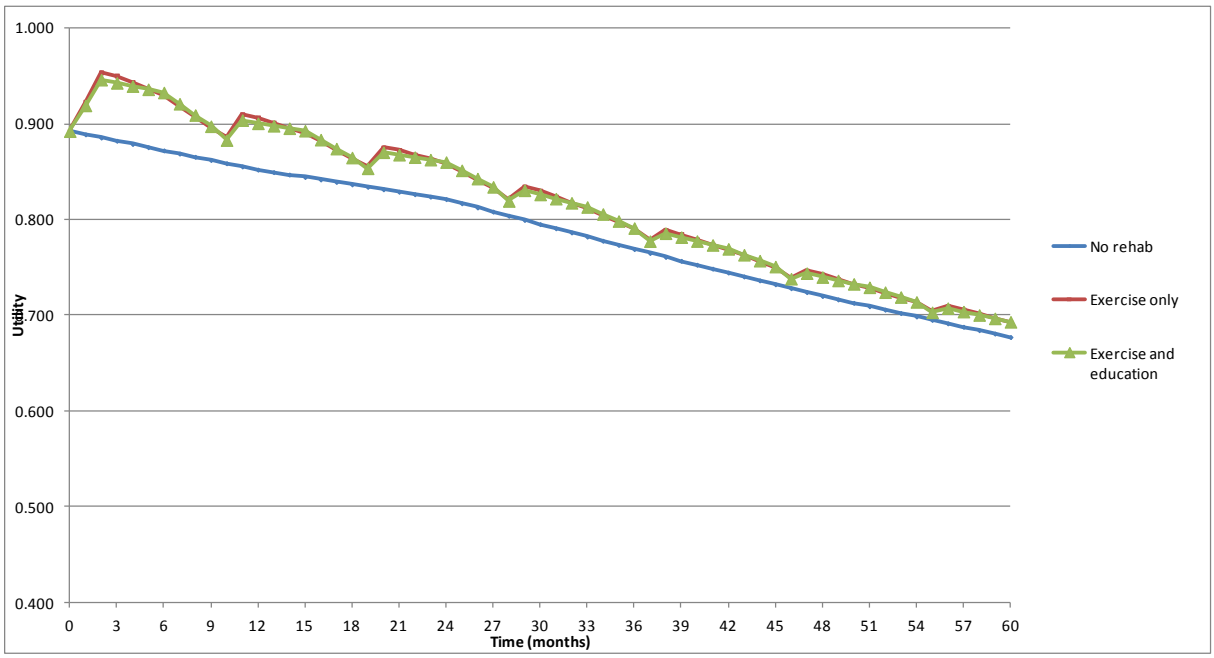
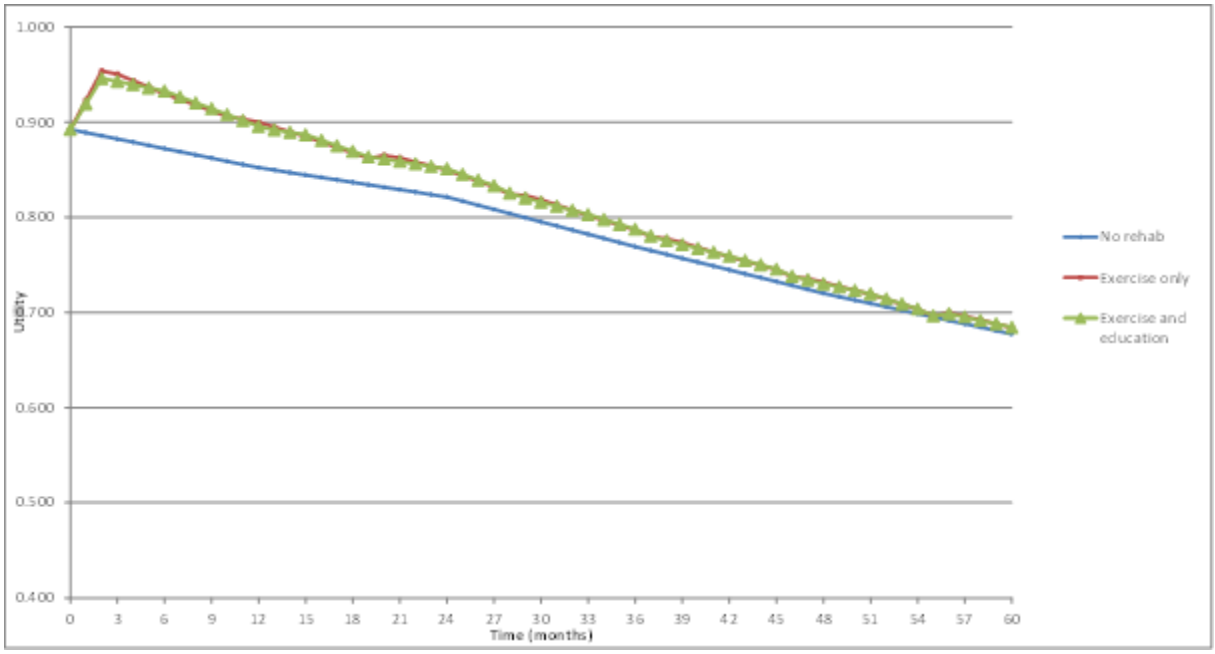


Figure 121: Utility estimates applied in the first 60 months of the model, whereby the pulmonary rehabilitation course was repeated at 9 months, and long term treatment effect duration of 24 months was applied. Each subsequent programme is 80% as effective as the previous programme experienced before.



L.2.3.6 Participation and drop out

The ability to participate in a programme will influence the cost effectiveness, however there was no evidence to inform this element of the model. The clinical experience of the group was that if the patient's needs were fully identified at assessment for pulmonary rehabilitation, it was likely that a patient would be able to fully participate throughout the course and experience any long term benefit effect thereafter. However, hospitalisation could influence a patient's ability to be "fit" to participate and subsequently benefit of pulmonary rehabilitation.

For this reason various participation scenarios were tested. The base case assumes so long as the patient is alive, they may participate in pulmonary rehabilitation, regardless of their hospitalised status. Participation scenario one assumes that a patient will not be able to participate or feel the benefit of pulmonary rehabilitation (i.e. their utility is the same as baseline) in the cycle post hospitalisation. Participation scenario two assumes that a proportion of the cohort could not return to participate in or benefit from pulmonary rehabilitation if they have had a previous hospitalisation. Within this scenario the proportion of patients with prior hospitalisation not returning to pulmonary rehabilitation was tested, from 100% of patients that had experienced hospitalisation not returning to the programme to 0% of patients (i.e. all patients could continue to participate which mirrored the base case participation setting). If a patient did not return to pulmonary rehabilitation, they would still be assessed (and incur assessment costs), however they would not incur programme costs or benefit from an improved quality of life from the programme.

L.2.3.7 Resource use and cost

There was no evidence identified that examined the impact pulmonary rehabilitaton may have on downstream healthcare resource use such as hospital admission or other healthcare contacts. Although in reality you would expect some costs to be associated with treatment, hospitalisation etc with no rehabilitation, there was no evidence to confirm whether these would be different from

those undertaking a rehabilitation programme. As such, no rehabilitation attracts no cost in the economic model.

The cost of the different rehabilitation programmes is calculated taking into account the level of resource use described in the different studies included in the clinical review. The unit costs of the key members of staff who may be involved with a pulmonary rehabilitation programme are outlined in Table 141. The base case uses the cost of the assessment and programme based on a costing using the key resource use defined by clinical members of the group. A sensitivity analysis uses the costs as presented by the NHS reference costs. A micro costing was preferred as the estimates provided by the NHS reference costs were considered high for this population group and likely to be reflective of a more specialised rehabilitation programme. The NHS reference costs used in the sensitivity analysis and for comparison are presented in Table 137

Table 137: 2010-11 NHS reference costs for travel (exclusive), pulmonary rehabilitation assessment (exclusive) and pulmonary rehabilitation (inclusive of assessment, but exclusive of travel).

Currency Code	Currency Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	No. Data Submissions
HTCS	Hospital Travel Cost Scheme	296,819	£12	£7	£15	71
DZ32Z	Simple Lung Function Exercise Testing (outpatient)	4,606	£269	£188	£263	49
VC01Z	Assessment for Rehabilitation (unidisciplinary) ('Non-specialist' Rehabilitation Services (NSRS) outpatient)	2,516	£241	£289	£289	2
VC03Z	Assessment for Rehabilitation (multidisciplinary; specialist) ('Non-specialist' Rehabilitation Services (NSRS) outpatient)	4,472	£209	£214	£214	2
CRTX	Community Rehabilitation	2,316,031	£71	£52	£87	84
VC40Z	Rehabilitation for Respiratory disorders ('Non-specialist' Rehabilitation Services (NSRS) - Bed Days: Admitted Patient Care)	51,695	£253	£223	£283	43

Costing of pulmonary rehabilitation course used in the base case analysis.

The setting of both the assessment and the programme was discussed, and in particular concerns for the patient safety were highlighted. The model assumes both the assessment and programme are conducted in a hospital outpatient setting; however, it is acknowledged that if appropriate assessment has been undertaken within a short time period of programme commencement, as well as appropriate standards of training and skills for the programme staff, a community setting could be viable. As the unit costs incorporate overheads and work space, the cost of the venue and equipment has not been included in the micro costing.

It was expected that the type of rehabilitation will also influence the number and type of NHS contacts a patient will make, for example number of GP home visits, number of GP surgery visits and number of hospitalisations. This is because it is expected that as patients learn how to manage their

symptoms, the number of NHS contacts will decrease. However, no data was found to inform this aspect of the planned model, and therefore this decrease in resource use has not been considered.

Two different approaches to costing were explored. The base case assumes the patient incurs the cost of the assessment and the course up front. This reflects the scenario of diminishing class size with drop out due to inability to participate due to disease progression, hospitalisation or death. A second approach assumes that the programme is rolling, with patients being able to participate at any time (i.e. have maximal benefit from the intervention throughout the time horizon of the model when participating) and that the class is at full capacity. This is presented as a scenario in the sensitivity analysis.

Assessment for pulmonary rehabilitation

Assessment for pulmonary rehabilitation is assumed to be the same for all programmes. It is assumed that patients would be referred for assessment following diagnosis at specialist MDT, and thereby the role of the MDT coordinator and ILD nurse will extend into this care pathway. Alternatively referral may come from Primary Care e.g. GPs, practice nurses, community pharmacists; and Secondary care e.g. consultants, nurses, Early Supported Discharge (ESD) teams; respiratory clinics, wards, physiotherapists. The Administration clerk will contact patients for assessment & re-assessment (and may need to send a follow-up letter to those who don't respond). This is assumed to take 10 minutes.

Clinical experts stressed the importance of the assessment for pulmonary rehabilitation. The IPF patient's desaturation profile should be fully understood at assessment in order to prevent an emergency scenario arising within the pulmonary rehabilitation class. Therefore both a submaximal and endurance test may be appropriate to ascertain the patient's needs when undertaking the course. It was agreed that the assessment should occur in a hospital setting so that in the unlikelihood of over exertion or emergency appropriate care would be available. To ensure access, the requirement for transport for a certain percentage of patients to be able to access the hospital outpatient setting is included in the costing. Using the group's experience, it was thought 10% of patients would require transport. It is assumed that oxygen requirements are already established and catered for, and as such oxygen assessment and oxygen use has not been included in the costing. It was acknowledged oxygen reassessment may be required within a short timeframe prior to the rehabilitation assessment. It was also assumed that lung function tests would have already been recently performed and were also not included in the assessment costs.

Clinical members advised that assessment would require 1.5 hours of a physiotherapist's time (band 6) due to the requirement for a practice exercise test and a real test, the need for the patient to rest between exercise tests and the need for the physiotherapist to be present throughout and conduct any associated paperwork. The same resource use will occur for first and repeat assessments. The costing assumes a frequency of 1.33 to allow for one third of patients to have more than one appointment (due to attendance failure or to complete the session).

Table 138: Unit cost of pulmonary rehabilitation assessment

Activity	Frequency	Cadre of staff	Band	Unit cost per hour	Time required (hour)	Group size	Cost per patient
Contacting patient for assessment	1.33	Clerical coordinator	4	26	0.17	1	6
Assessment	1.33	Physiotherapist	6	44	1.50	1	88
	0.13	Transport	na	19		1	3
						Total	**£96.13**

Pulmonary Rehabilitation Programme Costs

Nishiyama2008[355] gave a treatment effect for a nine week outpatient exercise program, with twice weekly supervised sessions. Exercise on treadmill at 80% of walking speed on initial 6-minute walk test, or on cycle ergometer at 80% of initial maximum workload. Strength training for limbs using elastic bands for approximately 20 minutes. Supplemental oxygen administered to achieve SpO2>90%. Some educational lectures were included but the content was not specified. Thus in the costing, we have the conservative assumption that both a nurse and physiotherapist (at band 6) are required throughout the course. In addition a clinician of registrar grade and two hospital based allied health professionals (at band 5) are each required to undertake an hour educational session per course programme. Transport is provided for 10% of patients. The costing of this programme is outlined in Table 139.

Table 139: Resource use for the programme cited by Nishiyama et al (2008)

Activity	Frequency	Cadre of staff	Band	Unit cost per hour	Time required (hour)	Group size	Cost per patient
Pulmonary Rehab Course	18	Physiotherapist - hospital	6	£44	0.50	10	£39
	18	Nurse (team leader) - hospital	6	£45	0.50	10	£41
	1	Band 5 allied hospital based allied work professional (i.e. hospital dietician)	5	£37	2.00	10	£7
	1	Registrar	na	£73	1.00	10	£7
	18	Transport	na	£12	1.00	10	£22
						Total	**£117.06**

Holland et al (2008) gave a treatment effect for an eight week outpatient exercise program, twice weekly supervised sessions consisting of 30 minutes endurance exercise (cycling and walking) with initial intensity at 80% of walking speed on initial 6-minute walk test and progressed according to protocol. Upper limb endurance and functional strength training for lower limbs also performed. Supplemental oxygen provided for SpO2>85%. Unsupervised home exercise program prescribed 3 times per week. In the costing, we have the conservative assumption that both a nurse and physiotherapist (at band 6) are required throughout the course. Transport is provided for 10% of patients. The costing of this programme is outlined in Table 140.

Table 140: Resource use for the programme cited by Holland et al (2008).

Activity	Frequency	Cadre of staff	Band	Unit cost per hour	Time required (hour)	Group size	Cost per patient
Pulmonary Rehab Course	16	Physiotherapist - hospital	6	£44	0.50	10.00	£35
	16	Nurse (team leader) - hospital	6	£45	0.50	10.00	£36

Activity	Frequency	Cadre of staff	Band	Unit cost per hour	Time required (hour)	Group size	Cost per patient
	16	Transport	na	£12	1.00	10.00	£20
						Total	**£91.02**

Table 141: Unit cost of NHS staff who may be involved with a pulmonary rehabilitation programme.

Staff	NHS Band	Hours per annum [a]	Direct salary [b]	On cost [c]	Qualification and on-going training [d]	Staff overhead [e]	Non staff overhead [f]	Capital [g]	Total	Per hour of working time
Hospital staff										
Hospital physiotherapist	6	1549	£29,464	£6,947	£4,927	£6,954	£15,147	£4,541	£67,980	£44
Hospital dietician	5	1549	£24,554	£5,789	£5,059	£5,796	£12,623	£3,535	£57,355	£37
Nurse team leader	6	1549	£29,464	£6,947	£9,356	£6,954	£15,147	£2,307	£70,175	£45
Registrar * PSSRU estimate for 2011 on mean full time equivalent earnings	-	1987	£55,600	£14,169	£28,711	£13,325	£29,024	£3,297	£144,126	£73
Clerical coordinator	4	1549	£20,433	£4,818	£0	£4,823	£10,504	£0	£40,578	£26

(a) Source: PSSRU (2011)[95]

(b) Source: For staff on NHS band pay scales these figures have been taken from 'Pay Circular (AfC) 2/2012'. Pay and conditions for NHS [352]. For consultants and the community pharmacist, these figures are taken from PSSRU (2011)[95] and have not been inflated.

*(c) Employers' national insurance is included plus 14 per cent of salary for employers' contribution to superannuation. This equates to approximately **24 per cent** of direct salary cost.*

*(d) Annual cost of qualification (estimated at **3.5 per cent** of total qualification cost), and where appropriate on-going training cost, is as reported by PSSRU (2011)[95]*

*(e) Direct overheads cover the resources required to deliver services to users or patients and are directly related to the level of service activity. Indirect overheads include functions of the organisation which support the services and allow the organisation to operate; examples would be the Human Resources or Finance Departments. Unfortunately, the information provided in the Summarised Accounts does not identify these categories separately, and we have adapted our estimation method to obtain a percentage figure that reflects the relationship between all overheads and direct salary costs. The Summarised Accounts show the number of care (direct) and non-care (indirect) staff and costs for the latter group were estimated using the average salary for NHS management and administrative staff[344] The calculation resulted in an additional **19.1 per cent** on care staff costs to cover management, estates and administrative staff.*

*(f) The non-staff overheads are the remaining costs to the provider (office costs, travelling subsistence, leased and contract hire, advertising, transport and moveable plant, telephone rentals etc.), supplies and services (clinical and general), utilities and premises costs (water, sewerage, electricity and gas, cleaning, air conditioning) and education and training costs for the professional staff. These account for an additional **41.6 per cent** of direct care staff salary costs, making a total of overheads 'multiplier' for direct salary costs of 60.7 per cent. More information on NHS accounting procedures can be found in the NHS Costing Manual [106 95]*

(g) Based on the new-build and land requirements, plus additional space for shared facilities. Capital costs have been annuitised over 60 years at a discount rate of 3.5 per cent (PSSRU 2011)[95]

L.2.4 Computations

The model was constructed in Microsoft Excel and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for mortality. Baseline utility was also time dependent and was conditional on the number of years post entry to the model.

Patients start in cycle 0 in an alive health state. Patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities and if the rate of disease progression indicated the patient should deteriorate to a state with a FVC% predicted value of less than 35%.

Transition probabilities for respiratory hospitalisation (including acute exacerbation) and death were derived from the literature. Transition probabilities for the rate of disease progression were based on an assumption of a fixed rate of decline in FVC% predicted for each subgroup. For mortality, hazard ratios for four risk factors within the same multivariate analysis were reported. However, as the regression equation, mean, variance and covariance matrix of beta coefficients from the regression equation was not obtained, it was not possible to calculate a composite hazard ratio to calculate the adjusted rate of mortality for the IPF patient given their respective risk factors. Instead, the risk calculator provided for an individual patient was used. These mortality rates were converted into transition probabilities for the respective cycle length (1 month in the base case) before inputting into the Markov model. For respiratory hospitalisation, the probability of the event over the time horizon specified by the literature was converted into a rate, before being converted into a probability appropriate for the cycle length. The above conversions were done using the following formulae:

$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where r = selected rate t= cycle length (months)
$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where P=probability of event over time t t=time over which probability occurs

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent (i.e. 1 month or 0.08 years) in the alive state of the model was weighted by a utility value that is dependent on the time spent in the model and the treatment effect. A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate = r). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. In the base case, rehabilitation costs were applied in cycle 1 only. If a difference in post-rehabilitation costs was being included, this was applied in cycle two and beyond. Costs were discounted to reflect time preference (discount rate = r) in the same way as QALYs using the following formula:

Discount formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: r = discount rate per annum n = time (years)

In the deterministic and probabilistic analysis, the total number of QALYs and resource costs accrued by each subgroup was recorded. These subtotals were summed across all subgroups to ascertain the

total number of patients in the population and the total QALYs and resource costs accrued for the population. The cost of a full pulmonary rehabilitation course was added to the recurrent cost of community pulmonary rehabilitation accrued over the time horizon of the model. The total cost and QALYs accrued by the cohort was divided by the number of patients in the population to calculate a cost per patient and cost per QALY.

L.2.4.1 Technical account of quality of life mapping methods

Where SF-36 dimension scores were reported, these were mapped onto the EQ5D index in order to approximate one generic preference based measurement for decision making. Via the method of moments [46], a beta distribution was fitted to each SF36 domain scores using the standard error and the number in the sample as reported by the study concerned.

A value was drawn from the SF36 domain scores' respective distributions to enter the algorithm EQ1 derived by Ara and Brazier (2008) [21] to estimate the mapped EQ5D index. If only baseline SF36 scores with absolute change over a time interval were reported, the absolute change was sampled from a normal distribution and added to the baseline domain score to calculate the follow up SF36 domain score to feed into the algorithm. Where available, SRGQ total scores were also mapped to EQ5D using the algorithm derived by Starkie et al (2011) [447].

Algorithm to map SF36 to EQ5D (Ara and Brazier, 2008) **EQ5D index** = 0.03256+0.0037***PH**+0.00111***RP**-0.00024***BP** +0.00024***GH** +0.00256***SF**-0.00063***RE** +0.00286***MH** +0.00052***V**	Where SF36 domains are indicated by: PH = Physical Health RP = Physical Role BP= Bodily Pain GH = General Health SF = Social Functioning RE = Emotional Role MH = Mental Health V= Vitality
Algorithm to map SGRQ to EQ5D (Starkie et al., 2010) **EQ5D index** = 0.9617 - **SGRQ** – (0.0001***SGRQ**^{2}) + 0.0231***Male**%	Where SGRQ = Total score Male% = Percentage of males

In the deterministic analysis, the best estimate of utility was calculated using the mean values reported by the study in the mapping algorithm. In the probabilistic analysis, each iteration drew from the sampled SF36 or SRGQ scores, which were then mapped to EQ5D by the appropriate algorithm. For the purpose of reporting the mapped EQ5D scores in this appendix, mapped values were calculated 20,000 times. The mean, standard deviation and upper and lower 95% confidence intervals of the 20,000 mapped EQ5D values were then calculated and reported.

L.2.4.2 Calculating cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs/QALYs(X) = total costs/QALYs for option X	• Cost-effective if: ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Benefit(X) = (QALYs\ (X) \times \lambda) - Costs\ (X)$$ *Where: Costs/QALYs(X) = total costs/QALYs for option X; λ = threshold*	• Cost-effective if: highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NMB was used to identify the optimal strategy in the probabilistic analysis simulations.

The probabilistic analysis was run for 10,000 simulations for the base case. Each simulation, total costs and total QALYs were calculated for each strategy. Net benefit was also calculated and the most cost-effective option identified (that is, the one with the highest net benefit), at a threshold of £20,000 per QALY gained. The results of the probabilistic analysis were summarised in terms of mean costs, mean QALYs and mean net benefit for each treatment option, where each was the average of the simulated estimates. The option with the highest mean net benefit (averaged across the simulations) was the most cost-effective at the specified threshold. The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

Results are also presented graphically where mean total costs and mean total QALYs for each strategy are plotted. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio, the magnitude of which is labelled.

L.2.5 Sensitivity analyses

A range of deterministic sensitivity analyses were completed to test the robustness of the results to changes in key inputs and assumptions. These are outlined in Table 142

Table 142: Deterministic Sensitivity Analyses

Heading	Description and rationale	Values used in deterministic
Structural settings		
SA1: discount rate	Differential discount rates were applied to costs and health benefits (measured in QALYs)	Cost discount rate of 1.5% QALY discount rate of 1.5%
Cohort settings		

Heading	Description and rationale	Values used in deterministic
SA2: age	We assume that the average age of patients commencing pulmonary rehabilitation is 70. However, this sensitivity analysis is conducted in the recognition that changes in identification and diagnosis of IPF may identify patients at earlier stages of disease progression and at a younger age. Results from this analysis inform whether prompt referral to pulmonary rehabilitation at an early diagnosis is more cost effective than a later referral.	40 years old 50 years old 60 years old 70 years old (base case) 80 years old
SA3: Starting FVC% predicted	We assume an initial FVC% predicted value for the cohort which one would hope to have at diagnosis of 100%. However, in recognition that diagnosis of IPF is often delayed, this assumption will be tested through sensitivity analysis with varying proportions of the cohort starting in the model with different FVC% predicted values. Results from this analysis inform whether prompt referral to pulmonary rehabilitation at an early stage of disease progression is more cost effective than a later referral.	100% 90% 80% 70% 60% 50%
SA4: The proportion in each subgroup.	The proportion of people with IPF experiencing a given rate of disease progression is uncertain, especially regarding the expected decline in patients who may in the first year in prognosis experience an increase in percentage predicted FVC% predicted. Therefore a sensitivity analysis was conducted to explore the impact a given rate of disease progression would have on the cost effectiveness of the intervention.	Base case: Stable = 57% (n=128) Moderate decline = 24% (n=54) Rapid decline = 19% (n=44)
SA4.1	Assumption that all patients with improved FVC% predicted experience same mortality risk as those with slow disease progression.	Stable = 69% (n=215) Moderate decline = 17% (n=54) Rapid decline = 14% (n=44)
SA4.2	Assumption that only patients with small improvement in FVC% predicted experience the same mortality risk as those with slow disease progression, and the remainder with a larger improvement in FVC experience the same mortality risk as those with moderate disease progression. This reflects the possibility that it is the degree of instability of FVC which could be prognostic.	Stable = 58% (n=183) Moderate decline = 27% (n=86) Rapid decline = 14% (n=44)
SA4.3	All patients offered pulmonary rehabilitation have stable disease	Stable: 100%
SA4.4	All patients offered pulmonary rehabilitation have moderate disease	Moderate: 100%
SA4.5	All patients offered pulmonary rehabilitation have rapid disease	Rapid: 100%
Participation assumptions		
Base case	The base case assumes that all patients who are alive can participate in pulmonary rehabilitation,	

Heading	Description and rationale	Values used in deterministic
	regardless of whether they have been hospitalised in the same cycle in which they may be undertaking rehabilitation.	
Participation scenario 1	In this scenario, we assume that patients cannot benefit from pulmonary rehabilitation in the cycle of hospitalisation. Treatment effect of pulmonary rehabilitation returns in the cycles post hospitalisation.	
Participation scenario 2 Base case	In this scenario, we assume that only a proportion of patients cannot participate or benefit from pulmonary rehabilitation post hospitalisation. For these patients the treatment effect of pulmonary rehabilitation does not return in the cycles post hospitalisation. They are costed for the assessment but not for any places on subsequent rehabilitation courses.	100%
		80%
		70%
		60%
		40%
		20%
		0% (base case participation effect)
Treatment effect scenarios		
SA5: Treatment effect duration (months)	This sensitivity analysis specifies the time period from the start of the programme until the treatment effect diminishes to baseline.	6 (base case)
		9
		12
		15
		18
		24
SA6: Treatment effect of repeated pulmonary rehabilitation programmes	This sensitivity analysis applies a treatment effect multiplier so that repeated programmes are proportionally less effective than the one undertaken previously.	100% as effective (base case)
		90% as effective
		80% as effective
		70% as effective
		60% as effective
		50% as effective
		40% as effective
		30% as effective
		20% as effective
		10% as effective
SA7: Time period between repeating the rehabilitation programme (months)	This sensitivity analysis examines the impact of varying the time period between the beginning of one programme and starting the subsequent programme.	6 months
		12 months (base case)
		18 months
		24 months
		36 months
		48 months
Intervention Cost and resource use		
SA.8: Use of NHS reference costs rather than micro costing	NHS reference costs (assumed to be inclusive of assessment) used instead of micro costing.	Community rehabilitation = £71 Respiratory rehabilitation = £253

Parameters associated with the programme composition and resource use (i.e. programme duration, staff levels, patients requiring transport) were not tested in a sensitivity analysis for two main reasons. Firstly adjustments were unlikely to make programme costs higher than those estimated through use of NHS reference costs and secondly the impact a change on resource use would have on programme effect is unknown.

L.2.6 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation. In particular, the median life expectancy calculated for the subgroups with differential rates of disease progression were of interest to the GDG. For this reason, survival curves calculated from the model were produced for clinical validation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist; this included systematic checking of the model calculations.

L.2.7 Interpreting results

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money[347].

In general, an intervention was considered to be cost effective if either of the following criteria applied:

a) The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As the analysis is based on two RCTs with a selected population and specified intervention it had limited applicability to the overall IPF population and current UK practice. It was felt that the analysis could help evaluate the likelihood that an offer of pulmonary rehabilitation at diagnosis, with continued community rehabilitation, was cost-effective and provide useful information to feed into decision making; however, it was also noted that it would not be able to provide definitive conclusions given these limitations.

L.3 Results

Detailed results are presented over the next few pages for the base case and various sensitivity analyses.

The results of the deterministic analyses showed the exercise and educational programme to be dominated by the exercise only programme, with the exercise only programme proving to be most cost effective at the £20,000 threshold throughout all analysis.

The results of the probabilistic analyses showed that the exercise and educational programme, and the exercise only programme, were comparable in their probability of being the optimal programme determined by the highest net monetary benefit, with no rehabilitation being the least optimal throughout.

L.3.1 Base case

The base case shows that pulmonary rehabilitation is cost effective when compared to no pulmonary rehabilitation, with both programmes having similar chance of being cost effective using the £20000 threshold when uncertainty of treatment effect is taken into account, with exercise programmes ranking optimal in 48% of simulations and exercise with education ranking optimal in 47% simulations. The highest incremental net benefit was achieved for the exercise programme of pulmonary rehabilitation. The results of the base case are shown in Figure 122, Figure 123 and Table 143.

Figure 122: Cost effectiveness plane for the base case results (deterministic)

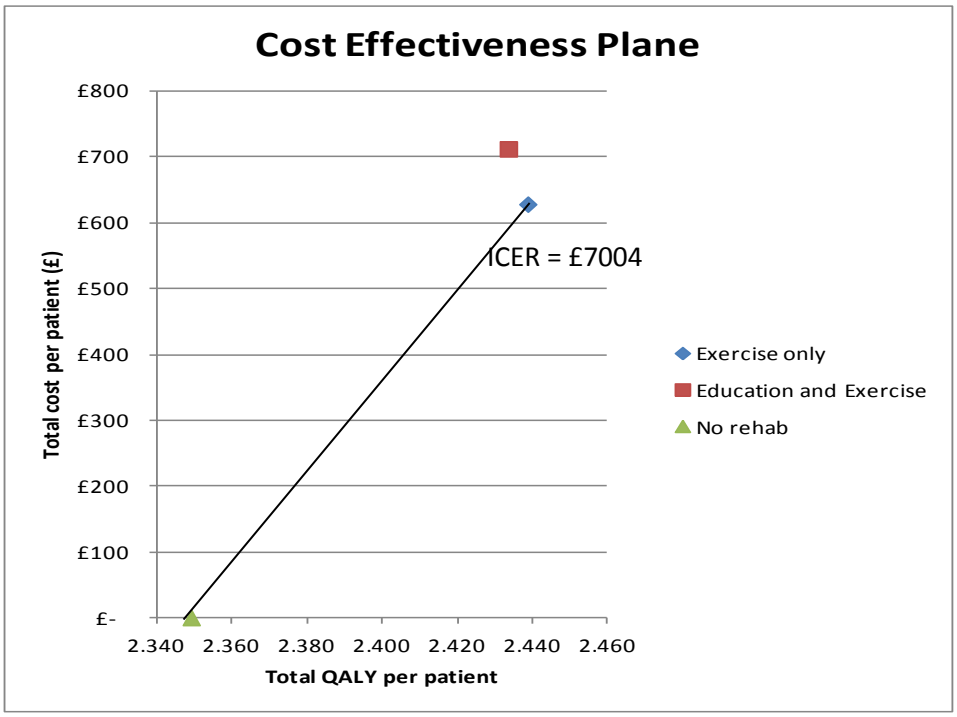


Figure 123: Cost effectiveness plane for the base case results (probabilistic)

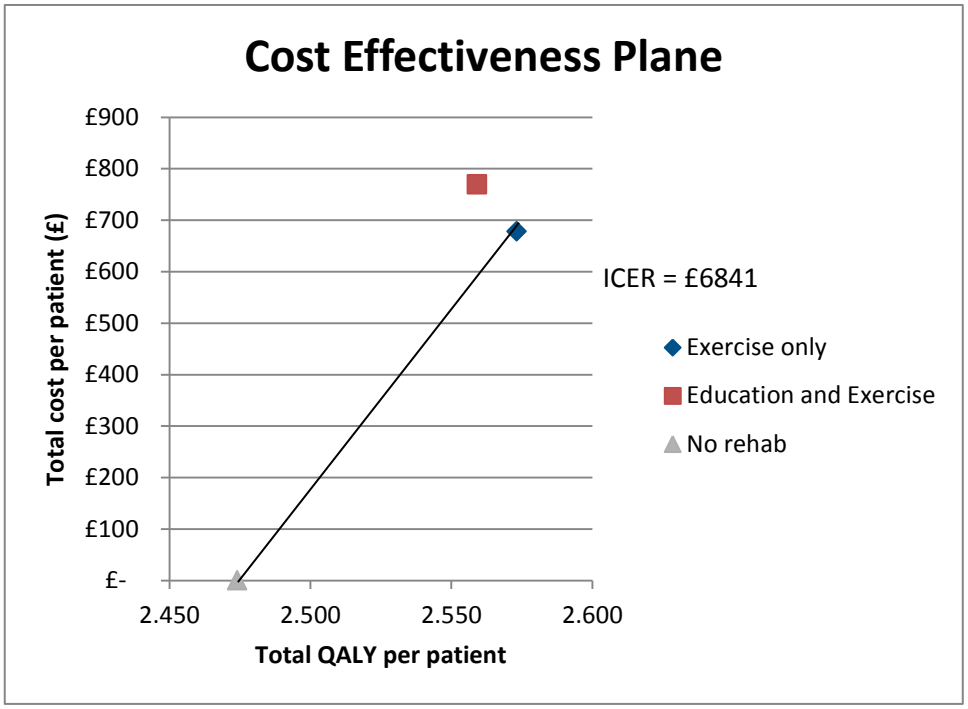


Table 143: Probabilistic results for the base case analysis, with results of sensitivity analysis looking at structural assumptions regarding participation and benefit post hospitalisation.

Participation scenarios	Intervention	Cost	Cost discounted	QALY	QALY discounted	NMB (£20K)	NMB (£30k)	% of times ranked optimal at 20K	% of times ranked optimal at 30K
Base case (a)	**No rehab**	£-	£-	2.713	2.474	£49,480	£74,220	5%	4%
	Exercise only	£741	£678	2.817	2.573	£50,785	£76,453	48%	48%
	Education and Exercise	£841	£770	2.802	2.559	£50,413	£75,933	47%	48%
Scenario 1 (b)	No rehab	£-	£-	2.713	2.474	£49,480	£74,220	6%	0%
	Exercise only	£741	£678	2.816	2.572	£50,676	£83,739	46%	51%
	Education and Exercise	£841	£770	2.801	2.558	£50,398	£83,204	48%	49%
Scenario 2 (c)	No rehab	£-	£-	2.713	2.474	£49,480	£74,220	6%	4%
	Exercise only	£741	£678	2.798	2.557	£50,457	£76,025	47%	48%
	Education and Exercise	£841	£770	2.785	2.544	£50,118	£75,562	47%	48%

(a) Base case participation scenario: Patients benefit from and participate in pulmonary rehabilitation regardless of hospitalisation.
(b) Participation scenario 1: Patients do not benefit from pulmonary rehabilitation in the cycle post hospitalisation
(c) Participation scenario 2: Patients do not benefit from or return to pulmonary rehabilitation post hospitalisation (all subsequent cycles) – however all patients undertake assessment regardless of previous hospitalisation.

L.3.2 Sensitivity analyses

L.3.2.1 Sensitivity analysis on structural assumptions regarding treatment effect and participation.

The results of the sensitivity analysis on different scenarios of participation are reported in Table 143. In no scenario was no rehabilitation optimal, and when only considering the mean net monetary benefit achieved the exercise only programme appeared more cost effective than the exercise and educational programme. It becomes more likely that the exercise only programme is cost effective in comparison to exercise and when patients are less likely to benefit from pulmonary rehabilitation post hospitalisation.

Participation scenarios were tested across all sensitivity analyses reported below to check that conclusions of the analysis did not change regardless of these baseline assumptions. The results from the sensitivity analyses using alternative participation scenarios did not indicate a different conclusion to the basecase. Due to this fact, and the quanity of results across all analyses, only the results from the basecase participation scenario are presented below.

L.3.2.2 Sensitivity analysis on differing rates of mortality post hospitalisation

Due the changes in treatment effect requiring a monthly cycle, the model took the conservative assumption by applying a higher mortality rate to patients who had experienced a respiratory hospitalisation, regardless of when that hospitalisation occurred. This assumption may reduce the number of patients who accumulate benefit of the programme once the programme has come to an end, favouring no rehabilitation.

To assess the impact this may have had on the potential life expectancy the model was rerun with a 6 month cycle, and a higher mortality rate was only applied in the cycle post hospitalisation. This allowed the scoring system presented by Du Bois in predicting mortality to be applied with greater accuracy; however the rate of movement through the health states slows with the longer cycle length. For information and clinical validation, Kaplan Meier curves for each cohort evaluated in this analysis were produced. These, alongside the mean and median life expectancy of each cohort are presented in Appendix M. Due to the changes in treatment effect requiring a cycle length less than 6 months, it was not possible to evaluate the potential increase in cost effectiveness of the pulmonary rehabilitation programmes that a change in this structural assumption may have.

If we assume only one hospitalisation per patient once diagnosed the results in Appendix M show that mortality is likely to be overestimated, and life expectancy is likely to be underestimated in the model. However, it is likely the model results are more reflective of the typical survival of people with IPF post diagnosis if people with IPF, once having experienced a respiratory hospitalisation, are likely to have a hospitalisation at least once every 6 months thereafter. When applying a higher mortality rate for only one month post hospitalisation, this favoured the pulmonary rehabilitation programmes in terms of cost effectiveness (see Table 145).

L.3.2.3 Sensitivity analysis of the discount factor

The change in discount factor did not change the conclusions of the analysis. Results are shown in Table 145.

L.3.2.4 Sensitivity analysis of the FVC% predicted and age

This analysis explored the impact that differing starting characteristics of the cohort may have on the cost effectiveness of the programme. The analysis shows that pulmonary rehabilitation in comparison to no rehabilitation is cost effective regardless of age of stage of disease progression. The exception is that the higher cost of the education and exercise programme meant it was not cost effective in cohorts which were older than 60 years of age and who also had an FVC% predicted baseline of 50%. In general, cost effectiveness is reduced in cohorts that have a higher starting risk of mortality and hospitalisation as these cohorts are less likely to accrue the benefit of the programme once it has ended. The deterministic results of this analysis are presented in Table 144.

For information and clinical validation, Kaplan Meier curves for each cohort evaluated in this analysis were produced. These, alongside the mean and median life expectancy of each cohort are presented in appendix M.

L.3.2.5 Sensitivity analysis on the proportion of people in each subgroup

The rate of disease progression of the cohort did not change the conclusions of the analysis, however the programmes are more cost effective when the cohort is more likely to be able to benefit from any long term treatment effect once the course has ended (i.e. with more stable rate of disease progression). Results are shown in Table 145.

L.3.2.6 Sensitivity analysis on the number of people able to rejoin and benefit from pulmonary rehabilitation post hospitalisation (extension of participation scenario 2)

The change in the number of people able to rejoin and benefit from pulmonary rehabilitation did not change the conclusions of the analysis. However, the programmes are more cost effective when the cohort is more likely to be able to benefit from any long term treatment effect once the course has ended (i.e. if more patients are able to experience a higher quality of life after pulmonary rehabilitation despite hospitalisation). Results are shown in Table 145.

L.3.2.7 Sensitivity analysis on the cost of the programme.

Use of NHS reference costs, which were higher for the educational programme than estimated through the costing of staff time, did not change the conclusion of the analysis. Results are shown in Table 145.

Table 144: Deterministic analysis of cost effectiveness according to FVC% predicted and age.

Starting FVC	Age	Mean number of cost per patient (£)						Mean number of QALYs gained per patient						Cost effectiveness				
		No rehab		Exercise only		Education and Exercise		No rehab		Exercise only		Education and Exercise		NMB (£20K)			ICER of intervention compared to no rehabilitation	
		Cost	Cost discounted	Cost	Cost discounted	Cost	Cost discounted	QALY	QALY discounted	QALY	QALY discounted	QALY	QALY discounted	No rehab	Exercise only	Education and Exercise	Exercise only	Education and Exercise
100%	40	£0	£0	£1,325	£1,152	£1,502	£1,307	4.75	4.14	4.94	4.32	4.93	4.31	£82,875	£85,277	£84,919	£6,482	£7,801
	50	£0	£0	£1,309	£1,141	£1,485	£1,296	4.68	4.10	4.87	4.28	4.86	4.27	£82,020	£84,413	£84,056	£6,458	£7,778
	60	£0	£0	£1,208	£1,064	£1,372	£1,209	4.33	3.83	4.51	3.99	4.50	3.98	£76,578	£78,819	£78,485	£6,438	£7,760
	70	£0	£0	£1,058	£944	£1,203	£1,073	3.82	3.41	3.97	3.55	3.96	3.55	£68,166	£70,141	£69,844	£6,466	£7,799
	80	£0	£0	£1,058	£944	£1,203	£1,073	3.82	3.41	3.97	3.55	3.96	3.55	£68,166	£70,141	£69,844	£6,466	£7,799
90%	40	£0	£0	£1,122	£998	£1,270	£1,130	4.15	3.68	4.31	3.83	4.30	3.82	£73,659	£75,672	£75,369	£6,626	£7,958
	50	£0	£0	£1,119	£995	£1,266	£1,128	4.13	3.67	4.29	3.82	4.28	3.81	£73,422	£75,435	£75,132	£6,615	£7,947
	60	£0	£0	£1,025	£921	£1,162	£1,045	3.78	3.39	3.93	3.53	3.92	3.53	£67,890	£69,775	£69,491	£6,567	£7,903
	70	£0	£0	£906	£823	£1,029	£935	3.34	3.02	3.47	3.15	3.46	3.14	£60,471	£62,148	£61,894	£6,583	£7,931
	80	£0	£0	£906	£823	£1,029	£935	3.34	3.02	3.47	3.15	3.46	3.14	£60,471	£62,148	£61,894	£6,583	£7,931
80%	40	£0	£0	£923	£839	£1,043	£949	3.53	3.18	3.65	3.31	3.64	3.30	£63,662	£65,291	£65,038	£6,800	£8,164

	50	£0	£0	£923	£839	£1,043	£949	3.53	3.18	3.65	3.31	3.64	3.30	£63,643	£65,272	£65,019	£6,799	£8,163
	60	£0	£0	£831	£764	£941	£866	3.14	2.87	3.26	2.98	3.25	2.97	£57,332	£58,831	£58,597	£6,751	£8,124
	70	£0	£0	£740	£685	£839	£777	2.76	2.54	2.87	2.64	2.86	2.63	£50,713	£52,046	£51,837	£6,786	£8,175
	80	£0	£0	£740	£685	£839	£777	2.76	2.54	2.87	2.64	2.86	2.63	£50,713	£52,046	£51,837	£6,786	£8,175
70%	40	£0	£0	£738	£687	£831	£774	2.95	2.71	3.04	2.80	3.04	2.80	£54,117	£55,331	£55,137	£7,228	£8,630
	50	£0	£0	£738	£687	£831	£774	2.95	2.71	3.04	2.80	3.04	2.80	£54,117	£55,331	£55,137	£7,228	£8,630
	60	£0	£0	£645	£606	£728	£684	2.51	2.33	2.60	2.41	2.59	2.41	£46,558	£47,646	£47,471	£7,154	£8,570
	70	£0	£0	£606	£571	£685	£646	2.32	2.16	2.40	2.24	2.40	2.23	£43,168	£44,199	£44,032	£7,133	£8,558
	80	£0	£0	£606	£571	£685	£646	2.32	2.16	2.40	2.24	2.40	2.23	£43,168	£44,199	£44,032	£7,133	£8,558
60%	40	£0	£0	£535	£510	£597	£570	2.27	2.12	2.33	2.19	2.33	2.18	£42,475	£43,234	£43,102	£8,045	£9,524
	50	£0	£0	£535	£510	£597	£570	2.27	2.12	2.33	2.19	2.33	2.18	£42,475	£43,234	£43,102	£8,045	£9,524
	60	£0	£0	£479	£460	£537	£515	1.95	1.84	2.00	1.89	2.00	1.89	£36,710	£37,408	£37,286	£7,940	£9,444
	70	£0	£0	£458	£440	£514	£495	1.82	1.72	1.87	1.77	1.87	1.77	£34,357	£35,028	£34,909	£7,920	£9,444
	80	£0	£0	£458	£440	£514	£495	1.82	1.72	1.87	1.77	1.87	1.77	£34,357	£35,028	£34,909	£7,920	£9,444
50%	40	£0	£0	£343	£334	£375	£366	1.57	1.50	1.59	1.52	1.59	1.52	£29,919	£30,115	£30,050	£12,608	£14,706
	50	£0	£0	£343	£334	£375	£366	1.57	1.50	1.59	1.52	1.59	1.52	£29,919	£30,115	£30,050	£12,608	£14,706
	60	£0	£0	£320	£313	£352	£345	1.38	1.33	1.41	1.35	1.40	1.35	£26,532	£26,722	£26,659	£12,441	£14,593
	70	£0	£0	£314	£307	£345	£339	1.32	1.27	1.34	1.29	1.34	1.29	£25,377	£25,565	£25,503	£12,416	£14,587

	80	£0	£0	£314	£307	£345	£339	1.32	1.27	1.34	1.29	1.34	1.29	£25,377	£25,565	£25,503	£12,416	£14,587

1 **Table 145: Deterministic results of sensitivity analyses testing assumptions and data sources of the model.**

	Mean cost per patient (£)						Mean number of QALYs gained per patient						Cost Effectiveness					
	No rehab		Exercise only		Education and Exercise		No rehab		Exercise only		Education and Exercise		NMB (£20K)			ICER of intervention when compared to no rehabilitation.		
Name of sensitivity analysis	Cost	Cost discounted	Cost	Cost discounted	Cost	Cost discounted	QALY	QALY discounted	QALY	QALY discounted	QALY	QALY discounted	No rehab	Exercise only	Education and Exercise		Exercise only	Education and Exercise
Base case	£0	£0	£672	£628	£762	£712	2.54	2.35	2.63	2.44	2.63	2.43	£46,972	£48,137	£47,949		£7,005	£8,427
No half cycle correction applied	£0	£0	£672	£628	£762	£712	2.58	2.38	2.67	2.47	2.66	2.46	£47,541	£48,731	£48,542		£6,907	£8,311
Discount rate of 1.5% applied to costs and 1.5% applied to benefits	£0	£0	£672	£652	£762	£739	2.55	2.46	2.63	2.55	2.63	2.54	£49,129	£50,262	£50,068		£7,309	£8,813
Sub grouping based on assumption all observed to have increasing FVC% predicted have slow disease progression	£0	£0	£741	£688	£839	£780	2.82	2.59	2.92	2.69	2.91	2.69	£51,823	£53,132	£52,925		£6,891	£8,287
Sub grouping based on assumption all observed to have increasing FVC% predicted have slow to moderate disease progression	£0	£0	£689	£643	£781	£729	2.62	2.42	2.71	2.51	2.71	2.51	£48,404	£49,606	£49,414		£6,972	£8,385
Cohort consists only of people **with slow disease progression**	£0	£0	£918	£844	£1,039	£957	3.53	3.22	3.66	3.35	3.65	3.34	£64,425	£66,108	£65,851		£6,680	£8,030
Cohort consists only of people **with moderate disease progression**	£0	£0	£418	£407	£473	£461	1.61	1.55	1.66	1.60	1.66	1.60	£30,977	£31,615	£31,501		£7,785	£9,357

Cohort consists only of people **with rapid disease progression**	£0	£0	£271	£268	£308	£305	0.81	0.79	0.84	0.82	0.83	0.82	£15,832	£16,132	£16,058		£9,442	£11,487
35% FVC% predicted cut off point for participation (no cut off point for participation)	£0	£0	£699	£649	£796	£739	2.54	2.35	2.64	2.45	2.64	2.44	£46,972	£48,304	£48,099		£6,554	£7,922
40% FVC% predicted cut off point for participation	£0	£0	£689	£642	£784	£730	2.54	2.35	2.64	2.44	2.63	2.44	£46,972	£48,240	£48,041		£6,721	£8,116
50% FVC% predicted cut off point for participation	£0	£0	£646	£605	£728	£683	2.54	2.35	2.63	2.43	2.62	2.43	£46,972	£48,044	£47,870		£7,218	£8,637
60% FVC% predicted cut off point for participation	£0	£0	£570	£538	£630	£596	2.54	2.35	2.60	2.41	2.60	2.41	£46,972	£47,681	£47,553		£8,629	£10,130
100% of patients do not return to or benefit from pulmonary rehabilitation post hospitalisation	£0	£0	£672	£628	£762	£712	2.54	2.35	2.62	2.42	2.61	2.42	£46,972	£47,868	£47,696		£8,242	£9,912
80% of patients do not return to or benefit from pulmonary rehabilitation post hospitalisation	£0	£0	£610	£569	£681	£636	2.54	2.35	2.62	2.43	2.62	2.42	£46,972	£47,980	£47,823		£7,216	£8,559
60% of patients do not return to or benefit from pulmonary rehabilitation post hospitalisation	£0	£0	£547	£510	£601	£561	2.54	2.35	2.62	2.43	2.62	2.43	£46,972	£48,093	£47,949		£6,259	£7,296
40% of patients do not return to or benefit from pulmonary rehabilitation post hospitalisation	£0	£0	£485	£452	£521	£485	2.54	2.35	2.63	2.43	2.62	2.43	£46,972	£48,205	£48,075		£5,362	£6,112
20% of patients do not return to or benefit from pulmonary rehabilitation post hospitalisation	£0	£0	£422	£393	£440	£410	2.54	2.35	2.63	2.44	2.63	2.43	£46,972	£48,318	£48,201		£4,521	£5,002
Higher mortality risk applied only one cycle post hospitalisation	£0	£0	£768	£707	£867	£799	2.96	2.69	3.06	2.79	3.05	2.79	£53,831	£55,115	£54,909		£7,106	£8,517
Cost of programme using NHS reference costs	£0	£0	£244	£229	£868	£815	2.54	2.35	2.63	2.44	2.63	2.43	£46,972	£48,535	£47,846		£2,556	£9,656

L.3.2.8 Sensitivity analysis on treatment effect duration, a declining treatment effect on each subsequent offer of pulmonary rehabilitation and time between repeated programmes of pulmonary rehabilitation.

There was no evidence to inform the duration of effect that pulmonary rehabilitation has on improving quality of life in people with pulmonary rehabilitation, with the longest reported follow up being 6 months, 4 months after the programme finished. [185]) As this study showed quality of life had not returned to baseline at this point, there is reason to believe that treatment effect lasts for a longer time period than 6 months, however the duration and rate of diminishing effect remains unknown. The optimal time between repeated offers of pulmonary rehabilitation to sustain a treatment effect given the additional cost of offering repeated programmes is dependent on the duration and rate of diminishing effect, as well as knowledge whether a repeated programme will achieve the same effect as the first programme the patient undertakes.

A three way sensitivity analysis was conducted to estimate the optimal time period between offers of repeated programmes given varying assumptions regarding duration and rate of diminishing long term treatment effect , and a potential decline in the magnitude of treatment effect with each additional programme. The analysis looked at repeating the programmes every 6, 12, 18, 24, 36 and 48 months, and identified which strategy (including no rehabilitation) obtained the highest net monetary benefit for a given combination treatment effect duration and magnitude of effect on repeated programmes. Table 146 details which strategy is optimal for a given combination of treatment effect assumptions, as well as the optimal time interval (in terms of highest net benefit) which the programme should be repeated for a combination of assumptions. An aspect of this analysis to keep in mind is that the more frequently the programme is repeated, the more programmes at a reduced efficacy (due to each subsequent programme having less effect) the patient will experience in the same timeframe. Further, when it is assumed that long term treatment effect is sustained over a lengthy time (i.e. 24 months), the repeated programme could give a lower treatment effect than what would have been observed at the same time point had the programme not been repeated.

Table 146: Optimal strategy given assumptions regarding treatment effect duration and the effectiveness of each subsequent programme

Treatment effect multiplier:		100%	90%	80%	60%	50%	40%	30%	20%	10%	0%
Treatment effect duration (months)	6	*Exercise programme, every 6 months*	*Exercise programme, every 12 months*	*Exercise programme, every 12 months*	*Exercise programme, every 18 months*	*Exercise programme, every 36 months*	*Exercise programme, every 48 months*	*Exercise programme, every 48 months*	*Exercise programme, every 48 months*	*Exercise programme, every 48 months*	*Exercise programme, every 48 months*
	9	*Exercise programme, every 6 months*	*Exercise programme, every 6 months*	*Exercise programme, every 12 months*	*Exercise programme, every 18 months*	*Exercise programme, every 18 months*	*Exercise programme, every 36 months*	*Exercise programme, every 48 months*	*Exercise programme, every 48 months*	*Exercise programme, every 48 months*	*Exercise programme, every 48 months*
	12	*Exercise programme, every 6 months*	*Exercise programme, every 12 months*	*Exercise programme, every 12 months*	*Exercise programme, every 12 months*	*Exercise programme, every 18 months*	*Exercise programme, every 36 months*	*Exercise programme, every 48 months*	*Exercise programme, every 48 months*	*Exercise programme, every 48 months*	*Exercise programme, every 48 months*
	15	*Exercise programme, every 6 months*	*Exercise programme, every 12 months*	*Exercise programme, every 12 months*	*Exercise programme, every 18 months*	*Exercise programme, every 18 months*	*Exercise programme, every 18 months*	*Exercise programme, every 36 months*	*Exercise programme, every 36 months*	*Exercise programme, every 48 months*	*Exercise programme, every 48 months*
	18	*Exercise programme, every 6 months*	*Exercise programme, every 12 months*	*Exercise programme, every 18 months*	*Exercise programme, every 18 months*	*Exercise programme, every 18 months*	*Exercise programme, every 18 months*	*Exercise programme, every 36 months*	*Exercise programme, every 36 months*	*Exercise programme, every 36 months*	*Exercise programme, every 48 months*
	24	*Exercise programme, every 12 months*	*Exercise programme, every 18 months*	*Exercise programme, every 18 months*	*Exercise programme, every 18 months*	*Exercise programme, every 18 months*	*Exercise programme, every 18 months*	*Exercise programme, every 36 months*	*Exercise programme, every 36 months*	*Exercise programme, every 36 months*	*Exercise programme, every 48 months*

The deterministic analysis shows that across the range of treatment effect assumptions tested, the exercise programme had the potential to produce the highest net benefit if offered at the optimal time interval. If the same treatment effect is observed on repeated offers, unless duration of treatment effect is very long (i.e. 24 months), it is most cost effective to repeat the programme every 6 months. If it is expected that each repeated programme is at least 80% as effective as the one previously undertaken, it is likely that repeating the programme every 12 months will be cost effective. This is with the exception when the treatment effect is likely to be less than 18 months. Once the magnitude of effect started to decrease by 60% on each subsequent programme the optimal time interval between programmes extends to 18 months or more. If the effectiveness of programmes more than halve on each offer, it is increasingly likely that the programme should not be repeated.

L.4 Discussion

L.4.1 Summary of results

It is highly likely that pulmonary rehabilitation compared to no rehabilitation is cost effective as a means to improve quality of life for people with IPF. It is uncertain whether pulmonary rehabilitation with exercise alone is cost effective when compared to a programme with an educational component, with both types of programmes having a comparable probability of being optimal in terms of cost effectiveness.

L.4.2 Limitations & interpretation

The conclusion that pulmonary rehabilitation compared to no rehabilitation proved to be robust over a wide range of sensitivity analyses. This gives reassurance that the conclusion of the analysis would not change had alternative assumptions in the model been made. However, the findings of the sensitivity analyses have practical implications in terms of how to make the programmes most cost effective and indicate the type of further research that could aid to resolve some of the limitations of the current model.

L.4.2.1 When and to whom to offer pulmonary rehabilitation

The two way sensitivity analysis on the age and FVC% predicted of the cohort as they entered the model showed that the programmes were most cost effective for patients who were likely to benefit from the longer term treatment effect. The sensitivity analysis on the proportion of patients in each subgroup of rate of disease progression supported this conclusion, with rehabilitation proving not cost effective for a cohort only consisting of people with rapid disease progression.

This finding has two implications for policy. Firstly, that an early diagnosis and referral to pulmonary rehabilitation is likely to improve the cost effectiveness of the programmes. Secondly, it is important to consider whether the patient group being referred to pulmonary rehabilitation is likely to able to experience the benefit of the course after it has ended, with a likely indicator of this being the patient's short term prognosis (i.e. whether the disease is progressing rapidly). However, the population diagnosed with IPF are heterogeneous and the disease course unpredictable. Because of this, recommendations that refer only specific subgroups to rehabilitation on the account of cost effectiveness are unlikely to be appropriate, and further may reduce the cost effectiveness of the programme as a whole due to delays in establishing a prognosis.

L.4.2.2 The optimal time interval between programmes

Generally, the longer the treatment effect duration the less cost effective it is to shorten the interval between programmes; and the less effective each subsequent offer is, the less cost effective it is to undertake the repeat programme.

If the programme is repeated frequently with a short time interval between programmes, the cohort will experience more programmes which are less effective than if there were less programmes in the same period of time (given each subsequent programme reduces in effect). For this reason repeating the programme every 6 months only becomes optimal if the effectiveness of each repeated programme is high and we assume the programme would not necessarily carry a long term treatment effect once the course ended. This scenario could be reflective of a maintenance exercise programme.

When a programme carries a longer term effect, it becomes more cost effective to have a longer time interval between programmes, especially if you assume each subsequent programme becomes less effective. This scenario could be reflective of an educational programme, where the knowledge gained would improve quality of life for a longer period, and unlikely to improve quality of life substantially if repeated.

In this population group, the natural history of the disease also plays a part in determining the optimal time period between programmes – which may in part explain why in some cases a more frequent programme is optimal despite an assumption that long term effect duration is longer. The impact of a reduced effect in each subsequent programme on results is mitigated to some extent by the fact the median life expectancy of people with IPF is relatively low and a low proportion of the cohort will start and participate in the less effective repeated programmes. If the life expectancy of people with IPF were to dramatically increase, the magnitude of effect of repeated programmes would be more influential on results.

The stable subgroup are most likely to be able to start, participate and benefit from repeated programmes, especially where there longer time intervals between programmes are explored. The analysis of FVC% predicted and age, as well as that for the subgroups, show it is the stable patients that potentially benefit most from pulmonary rehabilitation as they are most likely to be able to participate and accrue benefit after the programme has ended (due to reduced mortality and/or hospitalisation). The time period between programmes should therefore be sufficiently long to capitalise on any residing long term treatment effect, however should not be so long that the stable group which benefits most has become an age or entered a stage of disease progression (lower absolute FVC% predicted) where they have a higher risk of mortality or hospitalisation which would prevent them from benefiting from the long term treatment effect.

The probabilistic analysis suggested that the two types of programmes were equally as effective using the same treatment effect assumptions and when offered at the same time interval; however it is possible that one type of programme may carry a different long term effect than the other. If education has a longer treatment effect than the exercise programme, it would not be as cost effective as the exercise programme when offered in shorter time intervals. If this assertion is true, the practical implication is that the educational programme should be offered over a longer time period i.e. every 12 months, whereas an exercise programme should be repeated more regularly i.e. every 6 months.

L.4.2.3 The role of assessment for pulmonary rehabilitation

The assessment for pulmonary rehabilitation is of importance in determining which patients are most likely to benefit from pulmonary rehabilitation. An important factor to consider at assessment is whether a patient is likely to be able to benefit from the rehabilitation programme after the programme ends.

L.4.3 Summary of key limitations

It is likely that the model underestimates the cost effectiveness of the pulmonary rehabilitation programmes in the base case for a variety of reasons. Firstly, the mortality is likely to be overestimated in the base case, as demonstrated from the discrepancy in modelled life expectancy between the results using the base case settings and a higher risk of mortality applied only for 6 months post hospitalisation (see Appendix M:). A higher mortality would mean fewer patients will have benefited from long term treatment effect, and the programmes would appear less cost effective. It is worth noting however, the results shown in appendix M do not allow for a second hospitalisation. Secondly, the long term treatment effect in the base case was 6 months, and in practice this may be longer which would raise the cost effectiveness of the programme if offered at an appropriate time interval accordingly.

The quality of life assumed for people not undertaking rehabilitation was relatively high. In simulation runs where the educational programme had a large positive effect, it was possible the cohort experienced full health and any additional benefit beyond this was not captured, whereas it would have been if the quality of life associated with no rehabilitation was lower. Further, the quality of life improvement of the programmes may understate some important benefits described by patients (please refer to detail in the below sections).

The costing of the programme took the conservative assumption that only 10 patients would participate in each class, whereas in practice some class sizes may be greater than this, decreasing the cost per patient and improving the cost effectiveness of the programme. Further, we did not assume that rehabilitation influenced the number of healthcare contacts. If rehabilitation does reduce the number of healthcare contacts a patient makes, it could potentially be cost saving.

Thus although the model is robust in determining that rehabilitation is more cost effective than no rehabilitation through the incremental analysis, the exact accuracy of the total QALY gain and cost of the respective comparators is likely to be low.

L.4.3.1 Limitations of assumptions and simplifications made in order to model disease progression.

Subgroups are identified based upon their rates of disease progression at six months. It is assumed that the rate of disease progression at 6 months is indicative of future progression, and this rate is applied as a constant monthly probability throughout the model lifetime, with adjustment within subgroups to capture time-varying rates of progression. There is a strong assumption that the rate of disease is linear, posing a potential limitation in the validity of results.

In order to be as transparent as possible, median life expectancies and survival curves calculated by the models inputs are given in Appendix M. It is acknowledged that the median life expectancies given in Appendix M appear generally on the low side –e.g. a median life expectancy of 2.33 years for the population with 70% starting FVC% predicted (M.1 table 1) (cf. 2-5 years cited by Noble et al 2011 in the CAPACITY study[358]). However, as shown in the sensitivity analysis regarding age and starting FVC% predicted, as well as in section L.3.2.4 which details the natural history assumptions,

cost effectiveness is in general reduced in cohorts that have a higher starting risk of mortality and so these assumptions are unlikely to alter the conclusions of the analysis. In this regard the model is likely to make a conservative estimation of cost effectiveness.

L.4.3.2 Limitations of using FVC% predicted as a marker for disease progression in the IPF population, and as a proxy for ability to participate and benefit from the pulmonary rehabilitation programme.

Clinical members expressed concern in the use of FVC% predicted as a marker for disease progression in the IPF population, and as a proxy for ability to participate and benefit from the pulmonary rehabilitation programme. They felt that FVC% predicted was much less indicative of to reflect these factors than it may be for other populations which have a respiratory condition. However, given that the decline in FVC% predicted was found to be the best predictor of mortality (see chapter 6), and evidence was retrieved to link FVC to hospitalisation, a consensus was made it was suitable for modelling purposes.

Clinical members of the group noted that emphysema may mask disease progression if measured by FVC% predicted, and this co morbidity may in part explain why the baseline data to estimate the proportion of patients in each subgroup may have rises in FVC% predicted. There was insufficient data on clinical course and treatment effect to allow consideration of a subgroup of patients with IPF and emphysema, and it was not possible to explore whether these patients may benefit more from a pulmonary rehabilitation alongside COPD patients than IPF patients without the co morbidity.

L.4.3.3 Limitations of applying the same absolute treatment effect across all subgroups.

The treatment effect and baseline QoL was a mean taken across what developers assumed to be patients from all subgroups, An absolute, rather than a relative treatment effect was applied. The use of PSA explored the uncertainty surrounding this point estimate and the range covered may be indicative of the different rates of declines in the studies used to derive the inputs for the model. However it may not be reasonable to assume the same absolute QoL treatment benefit across all subgroups, with patients with varying rate of declines potentially benefiting more or less from pulmonary rehabilitation. Unfortunately, no evidence currently exists to inform how rate of decline may be correlated with outcomes of rehabilitation and as such developers felt a sensitivity analysis would not be useful. It was noted the subgroup sensitivity analysis could be misleading if the rate of disease progression did influence treatment outcome, however at this time developers felt there was not sufficient information to estimate the impact on conclusions. Overall, developers any range of inputs to modify the sensitivity analysis which would be estimated without further evidence unlikely to change final conclusions at this time.

L.4.3.4 Limitations of the instruments that measure quality of life in an IPF population

To our knowledge, validated instruments that measure quality of life in the IPF population are not in widespread use. However, the SF-36 generic HRQoL instrument and the SRGQ have been commonly used in clinical trials that have an IPF population. Both instruments have an evidence base to support their use in an IPF population [61 482 26 290,305,464,475,510] and scores from both instruments can be mapped to the EQ5D using standard methodology. However, a number of criticisms of the instruments for use in the IPF population exist.

The SF36 has been criticized for limited coverage of aspects that concern IPF patients [467]. For example the SF36 does not include any items focusing on therapy, sleep, forethought, employment and finances, dependence, sexual relations, or mortality. There is no mention of cough or breathlessness on the SF36, and pain which is included on the SF36 was not mentioned by IPF

patients. The SRGQ has also been criticized for limited coverage of aspects that concern IPF patients (in particular its lack of focus on social relationships), in addition to dubious face validity [104]. Overall the clinical members of the group felt that the HRQoL tools to assess QoL in IPF in the studies may not have captured all the important benefits that pulmonary rehabilitation may bring, for example reduced feeling of social isolation and improved social relationships. Such concerns have also been noted in the literature [104,467].

L.4.3.5 Limitations of mapping algorithms

The mapping function of SF-36 to EQ5D has been validated using a wide array of datasets from conditions such as asthma, coronary heart disease, diabetes, depression, renal transplant, pain, walking impairment, psoriasis etc. Authors of the algorithm note that caution should be taken when applying the algorithm for scores that are likely to produce very low utility values. They also note that a different algorithm may be preferable when looking at incremental differences between study arms or over time. However, when we have compared results from the two algorithms, the incremental difference calculated from the mean results from the first algorithm appears to be a closer match than the second.

The mapping function of the SRGQ score to EQ5D was developed using datasets for COPD patients, who were categorised by disease severity (moderate, severe, very severe). Authors found that the mapped QALY was slightly greater than the observed (Table 1).

Table 147: Mean (SD) observed and predicted utility scores by disease severity

Heading	Moderate	Severe	Very Severe
QALYs observed	2.16 (0.68)	1.99 (0.74)	1.75 (0.75)
QALYs predicted	2.18 (0.52)	2.01 (0.57)	1.80 (0.58)

The difference between the estimated QALY for the moderate and severe disease category was the same as the observed, however the estimated difference between the severe and very severe disease category was slightly smaller than observed. The difference in QALY gain between the most and least effective treatment was the same in predicted and observed values, however the authors note some of the ranking of strategies between these treatments changed. The mean values between observed and predicted did not differ more than 0.05, and each of the standard deviations associated with the mean value were greater than 0.05. It is likely that quality of life associated with more severe states may be lower than the mapped estimates suggest. Although uncertainty intervals will be provided with the mapped estimate, these will not be reflective of the potential error that may have been introduced by the mapping method.

L.4.3.6 Limitations regarding programme setting and resource use

A lack of clinical data meant that it was not possible to explore the cost effectiveness of rehabilitation in different settings. The potential settings of the pulmonary rehabilitation programmes include the outpatient, community and home setting, as well as potentially a residential course. The setting of the pulmonary rehabilitation programme could influence the cost of running the programme, accessibility for the patient and potentially the uptake and/or participation in the programme, and the efficacy of the programme.

It was expected that the type of rehabilitation would influence the number and type of NHS contacts a patient will make, for example number of GP home visits, number of GP surgery visits and number of hospitalisations. This is because it is expected that as patients learn how to manage their symptoms, the number of NHS contacts will decrease. However, no data was found to inform this aspect of the planned model, and therefore this decrease in resource use has not been considered. If

a healthcare resource use decrease is found with pulmonary rehabilitation, it is possible rehabilitation could be cost saving.

L.4.4 Comparisons with published studies

No economic evaluations comparing pulmonary rehabilitation programmes for patients with IPF to any other strategy was identified in the literature. One study in the UK, which was excluded at the sifting stage on the account of inappropriate population (predominately with COPD), found the programme to increase the mean number of QALYs generated by 0.03 per patient (p=0.03) and found a non-significant mean "cost saving" of £152 per patient (p=0.68). This study took into account potential reductions in healthcare resource use (such as GP visits) whereas the IPF model did not. Thus the cost effectiveness of rehabilitation for IPF patients appears lower despite the quality of life gain being similar and the cost per patient being higher than this models estimation (due to increased staff involvement on the programme). Even without reduction in healthcare resource use, however, the IPF model finds pulmonary rehabilitation to be cost effective using the £20,000 threshold.

L.4.5 Implications for future research

The economic model produced was based on many assumptions which future research may be able to inform. Future studies should consider the following to provide information which would improve future economic evaluations of pulmonary rehabilitation for people with IPF:

a) Collection of quality of life data using the EQ5D
b) The correlation between quality of life and any key outcomes of the study, such as change in FVC% predicted and walking distance achieved, with subsequent analysis adjusting for confounding factors appropriately.
c) Analysis of treatment effect and potential confounding factors such as stage and rate of disease progression.
d) Analysis of healthcare resource use with and without pulmonary rehabilitation.
e) Analysis of the factors which impact uptake, participation and sustaining treatment effect.
f) Analysis of the effectiveness of different types of pulmonary rehabilitation programme including that which could be shared with patients with COPD, with clear detail regarding the composition and setting of the programme, and resource use involved.
g) The duration and magnitude of the long term effect of pulmonary rehabilitation and the requirement of maintenance rehabilitation to sustain effect.

Only one economic model [171] evaluating a treatment strategy for people with IPF was identified to inform this guideline. In order for future economic models assessing any treatment strategy in this population group, information regarding the natural history of the disease, including information on prognostic risk factors for differing rates of disease progression and likelihood of acute exacerbation and/or respiratory hospitalisation is likely to improve future attempts at modelling the IPF disease pathway - which still remains relatively unknown.

L.4.6 Conclusion = evidence statement

It is highly likely that pulmonary rehabilitation is cost effective as a means to improve quality of life for people with IPF.

It is uncertain whether pulmonary rehabilitation with exercise alone is cost effective when compared to a programme with an educational component. Both programmes are highly likely to be cost effective when compared to no rehabilitation.

Pulmonary rehabilitation could be cost effective if offered at 6 to 12 month intervals to people with IPF, given appropriate assessment of the patient prior to the programme. If the duration of long term effect is shorter in the exercise programme than the educational programme, it is likely it is more cost effective to repeat this component of pulmonary rehabilitation in shorter time intervals (i.e. 6 months) than an educational component (i.e. 12 months or more).

Appendix M: Model produced Median and Mean Life Expectancies for people diagnosed with IPF

M.1 Median and mean life expectancy of people diagnosed with IPF

Table 148: Natural history results from the deterministic analysis in the model using base case assumptions and 1 month cycle length

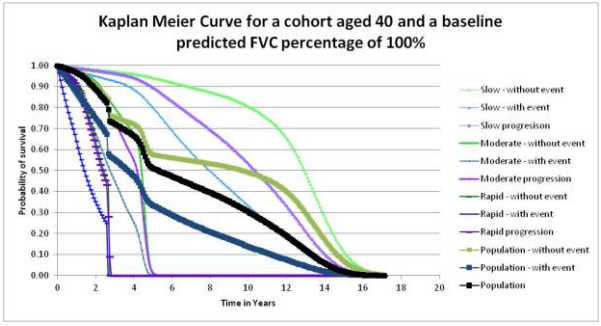
Starting FVC% predicted	Age	Median life expectancy				Mean Life years			
		Slow decline	Moderate decline	Rapid decline	Population	Slow decline	Moderate decline	Rapid decline	Population
100%	40	10.33	4.08	2.33	5.25	9.83	3.66	2.08	6.09
	50	10.25	4.08	2.33	5.25	9.60	3.66	2.08	6.09
	60	8.83	3.75	1.92	4.75	8.68	3.47	1.83	5.69
	70	7.25	3.25	1.67	4.33	7.40	3.10	1.67	4.97
	80	7.25	3.25	1.67	4.33	7.40	3.10	1.67	4.97
90%	40	8.83	3.50	2.00	4.08	8.33	3.09	1.75	5.51
	50	8.83	3.50	2.00	4.08	8.28	3.09	1.75	5.51
	60	7.42	3.25	1.58	4.00	7.36	2.90	1.54	5.02
	70	6.08	2.75	1.33	3.58	6.31	2.63	1.38	4.37
	80	6.08	2.75	1.33	3.58	6.31	2.63	1.38	4.37
80%	40	7.33	2.92	1.67	3.33	6.86	2.50	1.41	4.72
	50	7.33	2.92	1.67	3.33	6.86	2.50	1.41	4.72
	60	5.92	2.67	1.25	3.17	5.91	2.31	1.24	4.12
	70	5.00	2.25	1.00	2.83	5.07	2.12	1.07	3.58
	80	5.00	2.25	1.00	2.83	5.07	2.12	1.07	3.58
70%	40	5.92	2.25	1.33	2.75	5.53	1.96	1.07	3.81
	50	5.92	2.25	1.33	2.75	5.53	1.96	1.07	3.81
	60	4.42	2.17	1.00	2.42	4.50	1.88	0.95	3.18
	70	4.08	1.83	0.75	2.33	4.18	1.67	0.80	2.92
	80	4.08	1.83	0.75	2.33	4.18	1.67	0.80	2.92
60%	40	4.33	1.67	0.92	1.92	4.05	1.48	0.80	2.80
	50	4.33	1.67	0.92	1.92	4.05	1.48	0.80	2.80

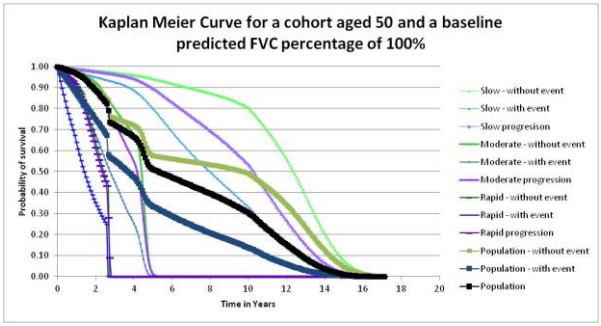
	60	3.42	1.58	0.83	1.75	3.36	1.41	0.72	2.38
	70	3.00	1.50	0.58	1.67	3.16	1.28	0.61	2.22
	80	3.00	1.50	0.58	1.67	3.16	1.28	0.61	2.22
50%	40	2.83	1.00	0.58	1.25	2.70	0.97	0.52	1.86
	50	2.83	1.00	0.58	1.25	2.70	0.97	0.52	1.86
	60	2.50	1.00	0.58	1.08	2.34	0.92	0.49	1.64
	70	2.42	0.92	0.42	1.08	2.26	0.86	0.42	1.57
	80	2.42	0.92	0.42	1.08	2.26	0.86	0.42	1.57

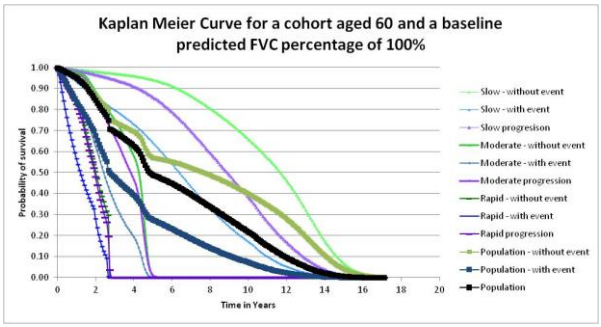
Table 149: Natural history results from the deterministic analysis in the model using base case assumptions, but with a 6 month cycle length and application of the higher post hospitalisation mortality risk only in the cycle of hospitalisation

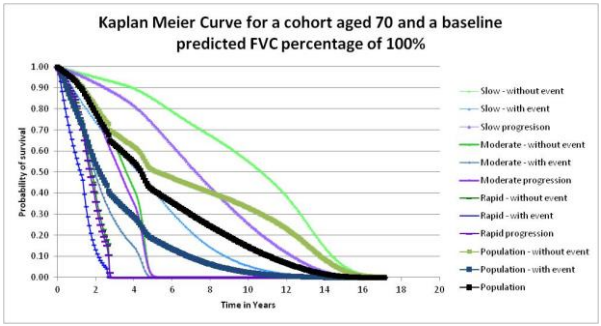
Starting FVC% predicted	Age	Median life expectancy				Mean Life years			
		Slow decline	Moderate decline	Rapid decline	Population	Slow decline	Moderate decline	Rapid decline	Population
100%	40	14.50	4.00	2.00	8.00	13.78	3.97	2.18	9.18
	50	13.50	4.00	2.00	8.00	13.09	3.97	2.18	8.79
	60	12.50	4.00	2.00	7.00	12.37	3.80	1.94	8.29
	70	11.00	3.50	1.50	4.50	10.78	3.39	1.80	7.26
	80	11.00	3.50	1.50	4.50	10.78	3.39	1.80	7.26
90%	40	12.00	3.00	1.50	6.50	11.57	3.34	1.81	7.71
	50	12.00	3.00	1.50	6.50	11.29	3.34	1.81	7.54
	60	10.50	3.00	1.50	5.00	10.20	3.17	1.62	6.85
	70	9.00	3.00	1.50	4.00	8.96	2.86	1.49	6.05
	80	9.00	3.00	1.50	4.00	8.96	2.86	1.49	6.05
80%	40	10.00	2.50	1.50	4.50	9.32	2.72	1.48	6.21
	50	10.00	2.50	1.50	4.50	9.26	2.72	1.48	6.18
	60	8.00	2.50	1.00	3.50	7.95	2.58	1.35	5.38
	70	7.00	2.50	1.00	3.00	7.05	2.35	1.25	4.80
	80	7.00	2.50	1.00	3.00	7.05	2.35	1.25	4.80
70%	40	7.50	2.00	1.00	3.50	7.30	2.11	1.19	4.87
	50	7.50	2.00	1.00	3.50	7.30	2.11	1.19	4.87
	60	6.00	2.00	1.00	2.50	5.90	1.99	1.09	4.03
	70	5.50	1.50	1.00	2.00	5.61	1.83	0.98	3.81
	80	5.50	1.50	1.00	2.00	5.61	1.83	0.98	3.81
60%	40	5.50	1.50	0.50	2.50	5.27	1.54	0.87	3.52
	50	5.50	1.50	0.50	2.50	5.27	1.54	0.87	3.52
	60	4.50	1.00	0.50	1.50	4.32	1.48	0.81	2.96
	70	4.00	1.00	0.50	1.50	4.25	1.35	0.73	2.87
	80	4.00	1.00	0.50	1.50	4.25	1.35	0.73	2.87
50%	40	3.00	0.50	0.50	1.50	3.29	1.01	0.62	2.23
	50	3.00	0.50	0.50	1.50	3.29	1.01	0.62	2.23
	60	2.50	0.50	0.50	1.00	2.83	0.96	0.59	1.94
	70	2.50	0.50	0.00	1.00	2.80	0.90	0.51	1.90
	80	2.50	0.50	0.00	1.00	2.80	0.90	0.51	1.90

Figure 124: Kaplan Meier curves produced by using the base case probabilities of the economic model (1 month cycle)









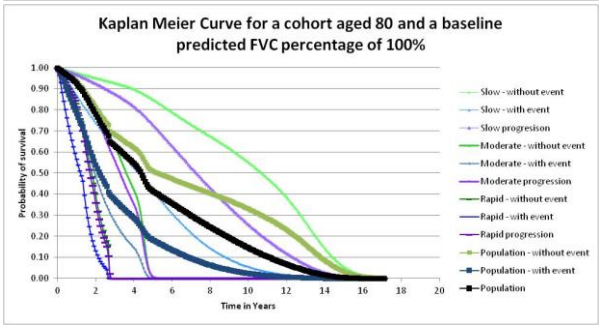
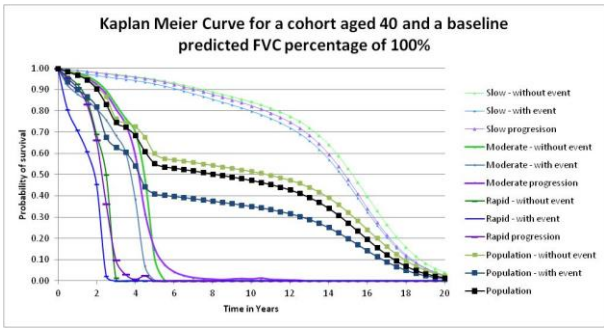
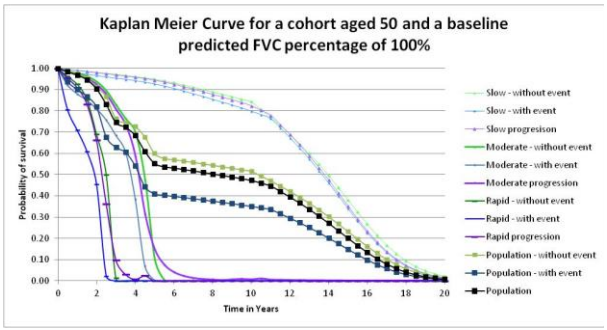
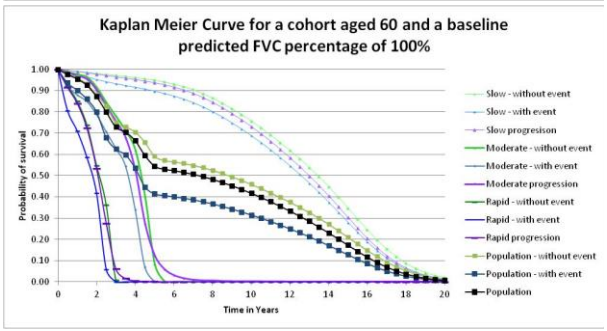
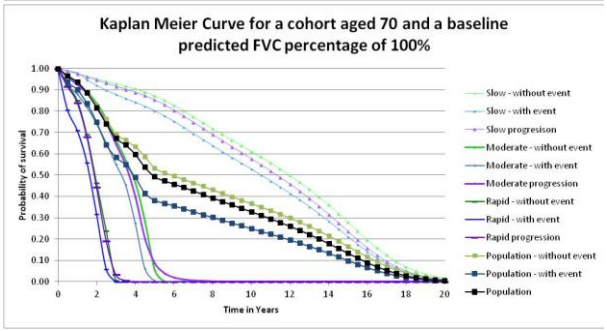


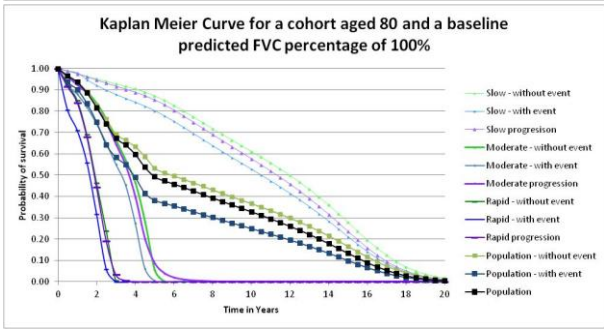
Figure 125:Kaplan Meier curves produced by using the higher risk of hospitalisation for only one cycle post hospitalisation (6month cycle)

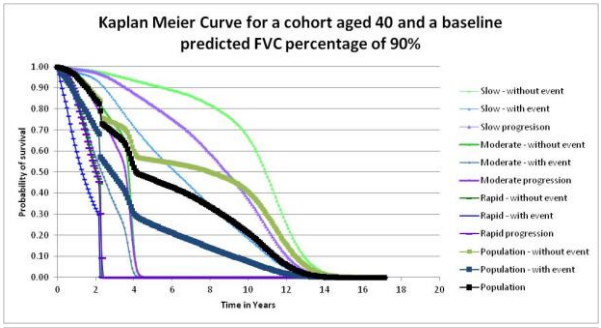


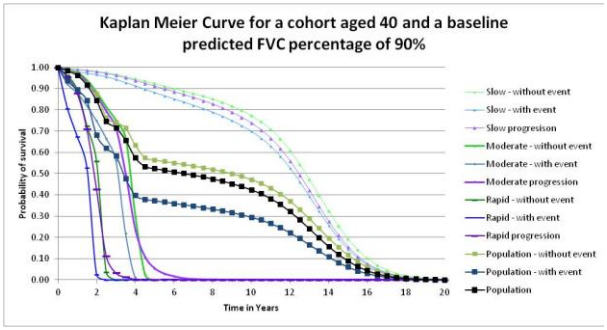


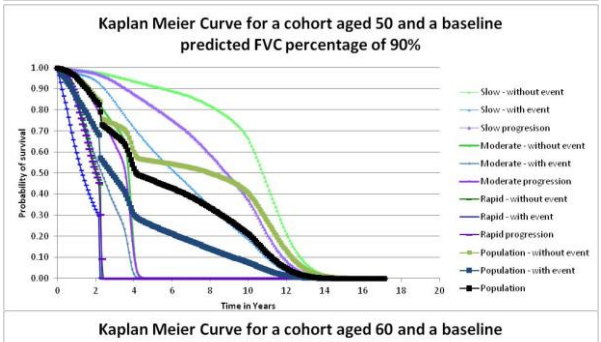


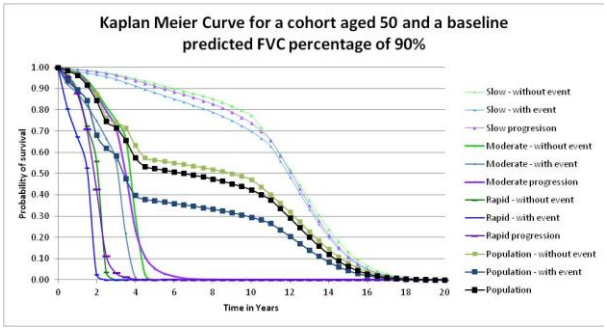


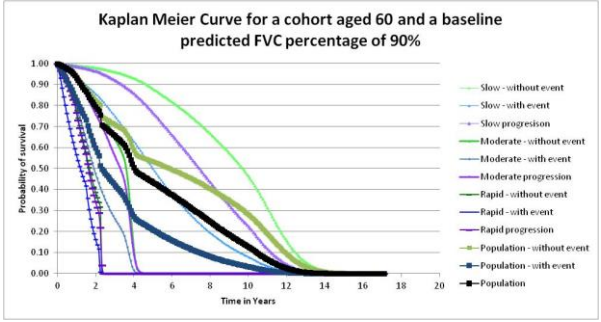


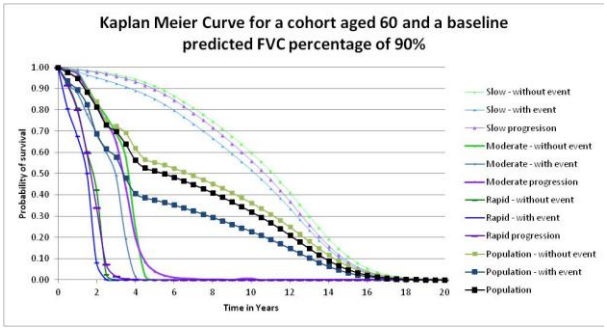

Kaplan Meier Curve for a cohort aged 40 and a baseline predicted FVC percentage of 90%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

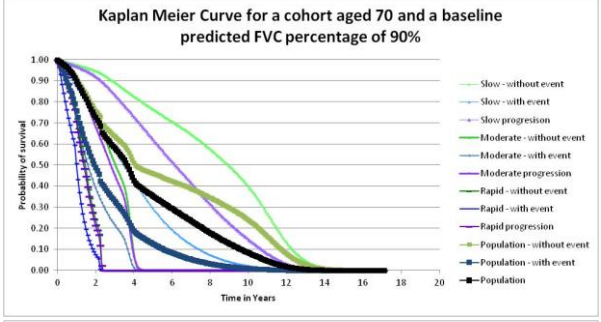

Kaplan Meier Curve for a cohort aged 40 and a baseline predicted FVC percentage of 90%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

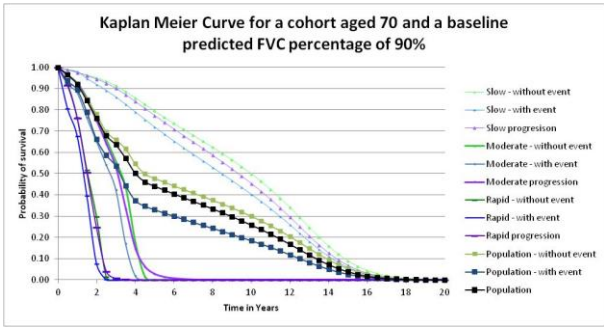

Kaplan Meier Curve for a cohort aged 50 and a baseline predicted FVC percentage of 90%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

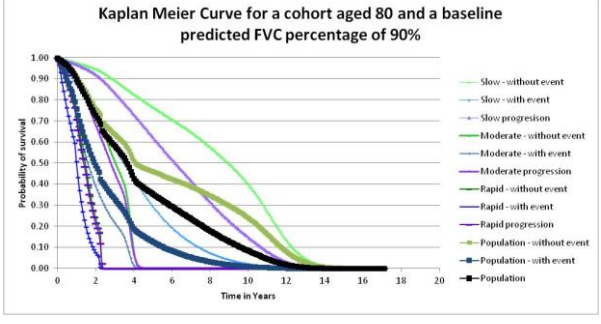

Kaplan Meier Curve for a cohort aged 50 and a baseline predicted FVC percentage of 90%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

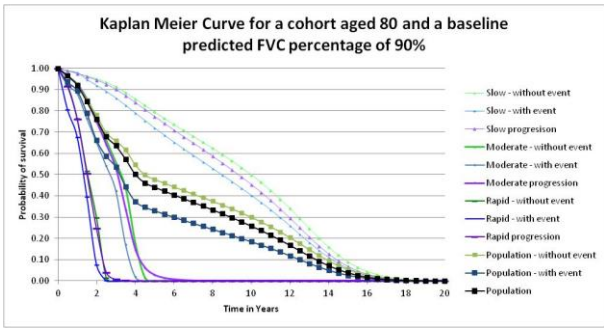

Kaplan Meier Curve for a cohort aged 60 and a baseline predicted FVC percentage of 90%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

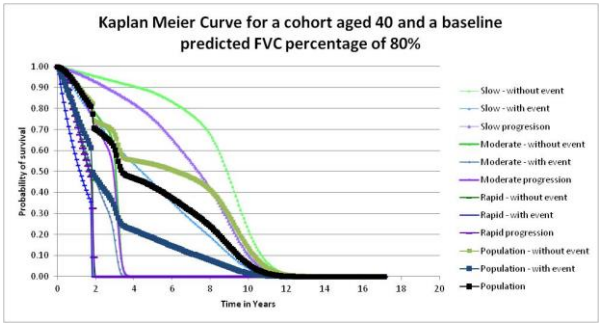

Kaplan Meier Curve for a cohort aged 60 and a baseline predicted FVC percentage of 90%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

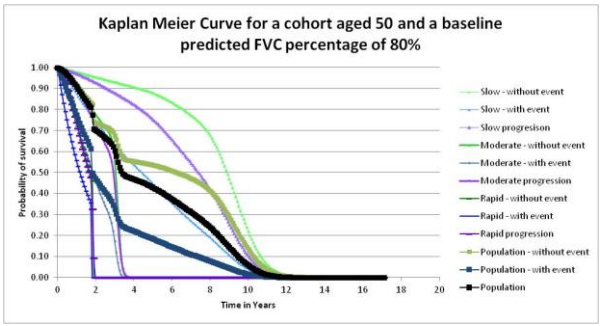

Kaplan Meier Curve for a cohort aged 70 and a baseline predicted FVC percentage of 90%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

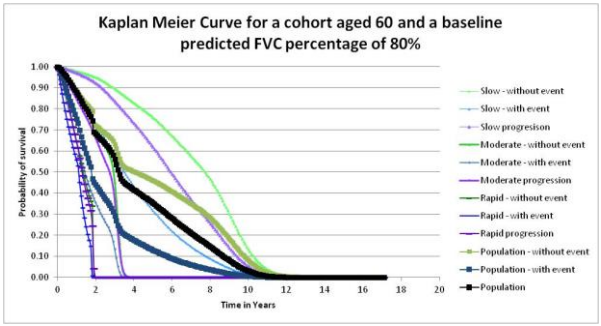

Kaplan Meier Curve for a cohort aged 70 and a baseline predicted FVC percentage of 90%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

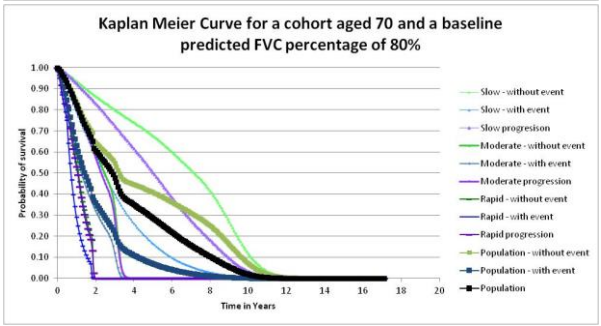

Kaplan Meier Curve for a cohort aged 80 and a baseline predicted FVC percentage of 90%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

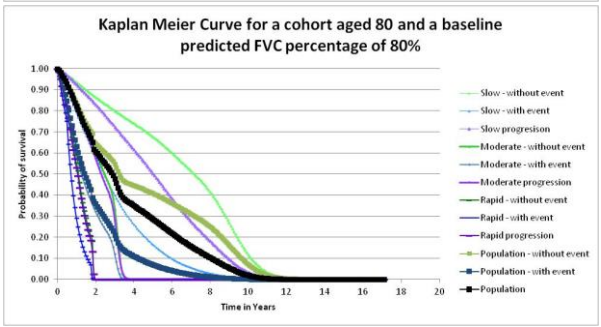

Kaplan Meier Curve for a cohort aged 80 and a baseline predicted FVC percentage of 90%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

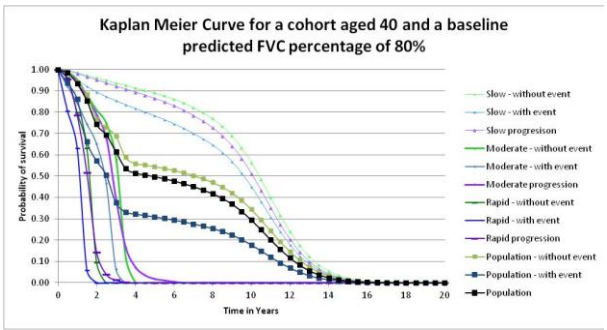

Kaplan Meier Curve for a cohort aged 40 and a baseline predicted FVC percentage of 80%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

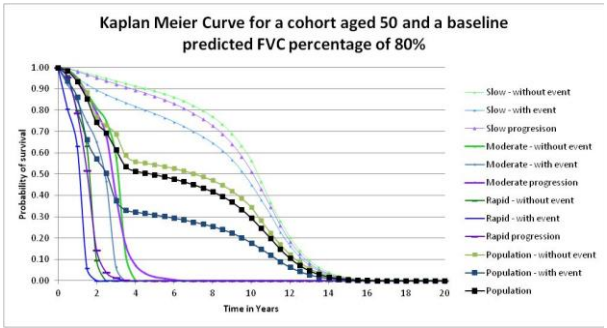

Kaplan Meier Curve for a cohort aged 50 and a baseline predicted FVC percentage of 80%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

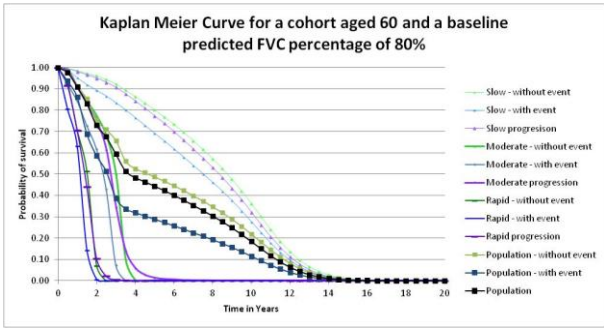

Kaplan Meier Curve for a cohort aged 60 and a baseline predicted FVC percentage of 80%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

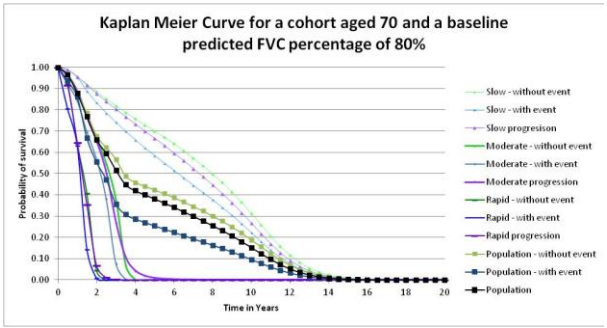

Kaplan Meier Curve for a cohort aged 70 and a baseline predicted FVC percentage of 80%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

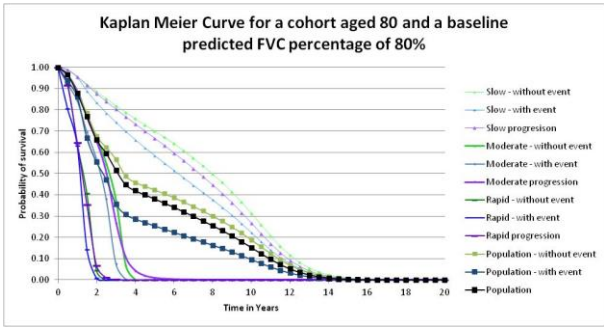

Kaplan Meier Curve for a cohort aged 80 and a baseline predicted FVC percentage of 80%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

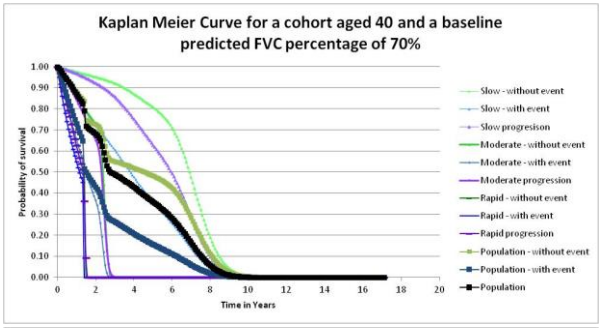

Kaplan Meier Curve for a cohort aged 40 and a baseline predicted FVC percentage of 80%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

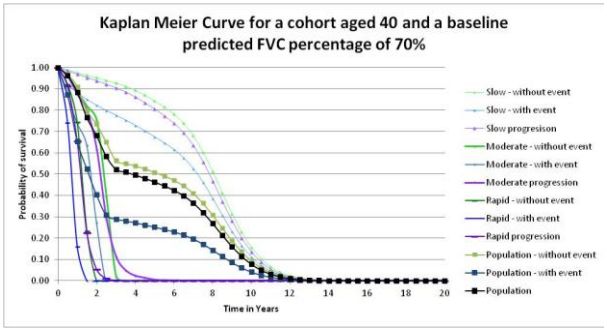

Kaplan Meier Curve for a cohort aged 50 and a baseline predicted FVC percentage of 80%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

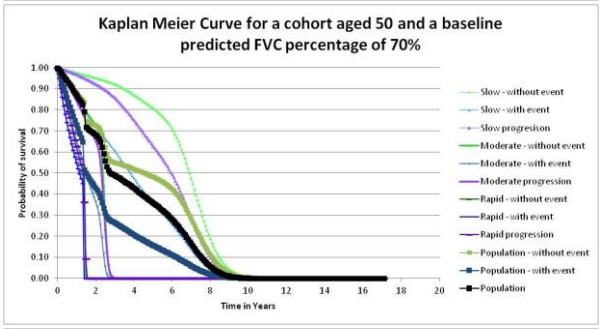

Kaplan Meier Curve for a cohort aged 60 and a baseline predicted FVC percentage of 80%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

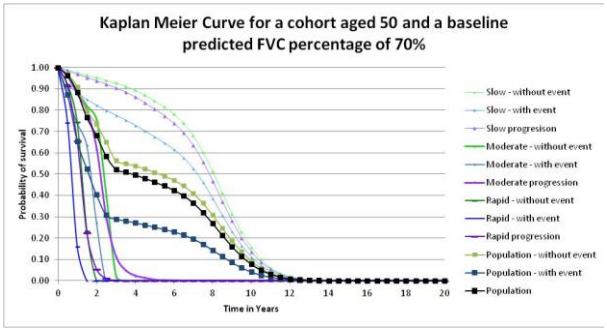

Kaplan Meier Curve for a cohort aged 70 and a baseline predicted FVC percentage of 80%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

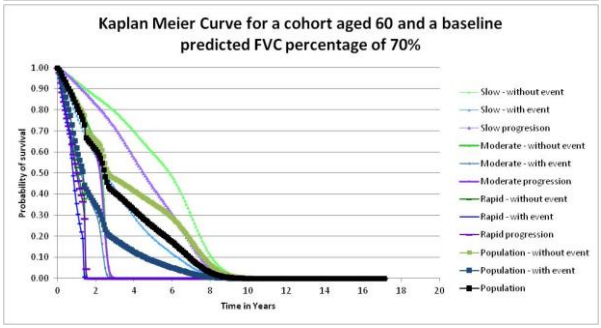

Kaplan Meier Curve for a cohort aged 80 and a baseline predicted FVC percentage of 80%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

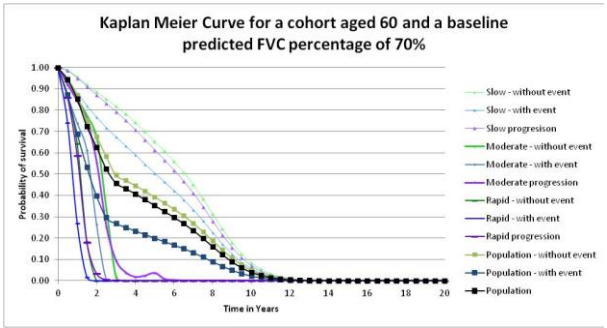

Kaplan Meier Curve for a cohort aged 40 and a baseline predicted FVC percentage of 70%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

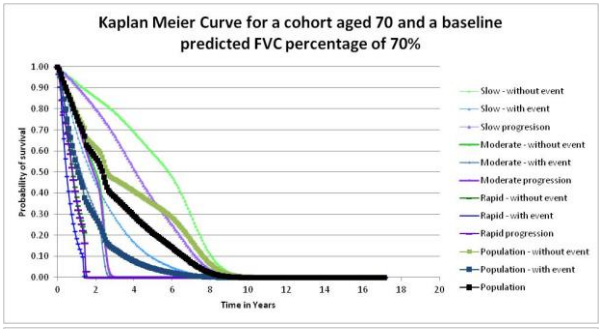

Kaplan Meier Curve for a cohort aged 40 and a baseline predicted FVC percentage of 70%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

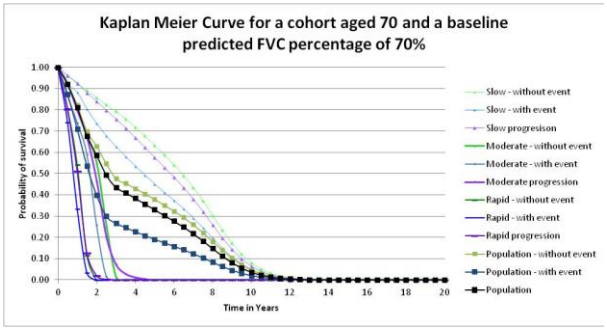

Kaplan Meier Curve for a cohort aged 50 and a baseline predicted FVC percentage of 70%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

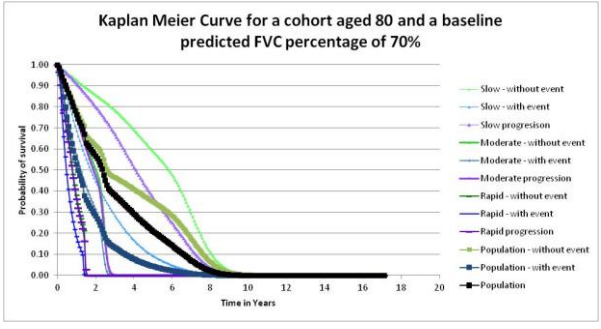

Kaplan Meier Curve for a cohort aged 50 and a baseline predicted FVC percentage of 70%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

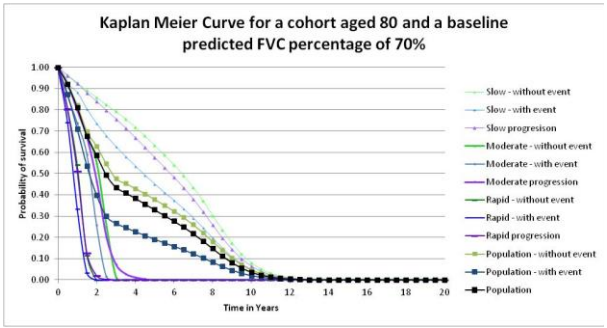

Kaplan Meier Curve for a cohort aged 60 and a baseline predicted FVC percentage of 70%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

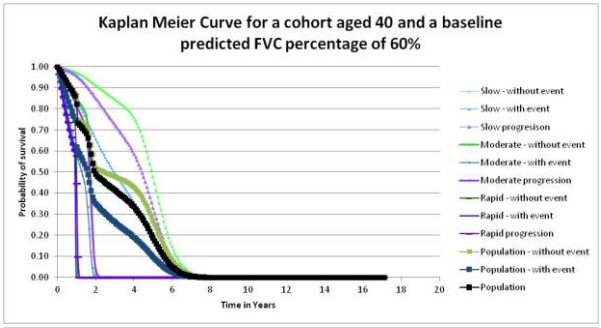

Kaplan Meier Curve for a cohort aged 60 and a baseline predicted FVC percentage of 70%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

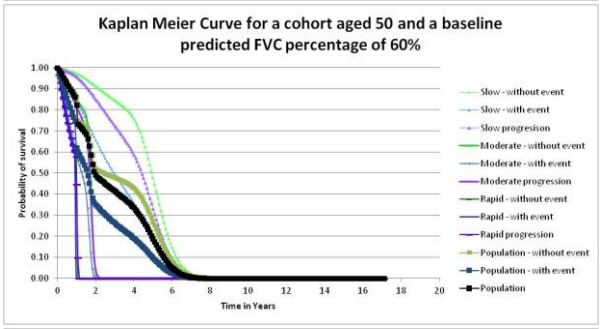

Kaplan Meier Curve for a cohort aged 70 and a baseline predicted FVC percentage of 70%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

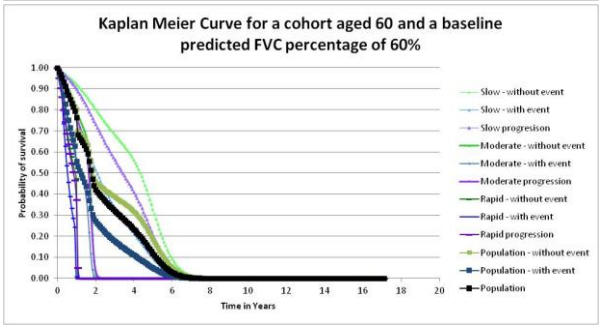

Kaplan Meier Curve for a cohort aged 70 and a baseline predicted FVC percentage of 70%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

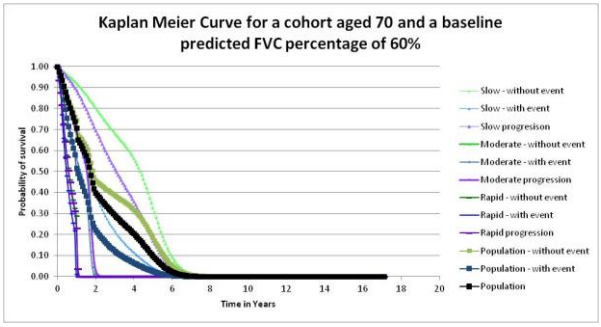

Kaplan Meier Curve for a cohort aged 80 and a baseline predicted FVC percentage of 70%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

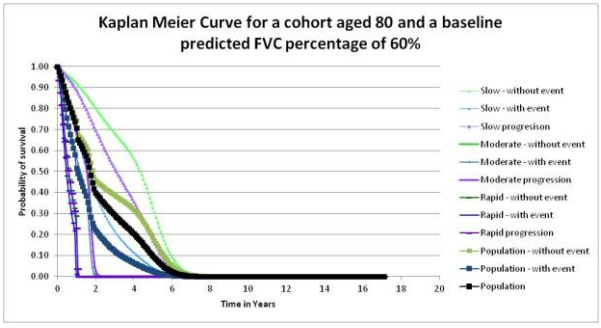

Kaplan Meier Curve for a cohort aged 80 and a baseline predicted FVC percentage of 70%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

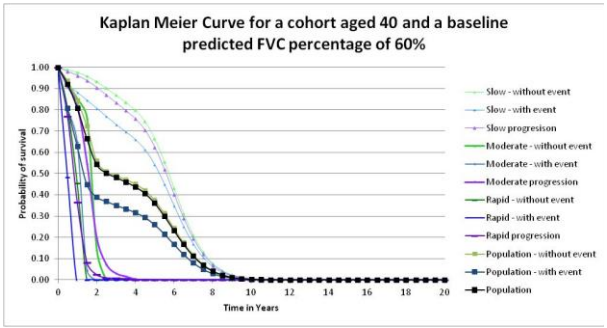

Kaplan Meier Curve for a cohort aged 40 and a baseline predicted FVC percentage of 60%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

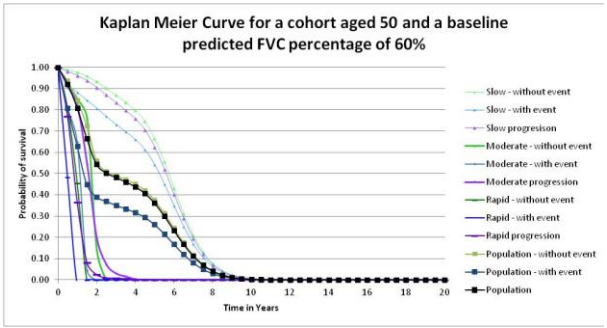

Kaplan Meier Curve for a cohort aged 50 and a baseline predicted FVC percentage of 60%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

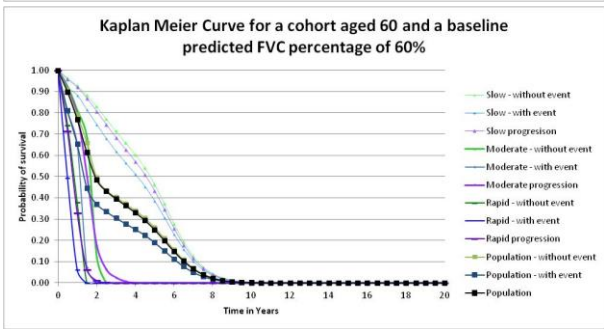

Kaplan Meier Curve for a cohort aged 60 and a baseline predicted FVC percentage of 60%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

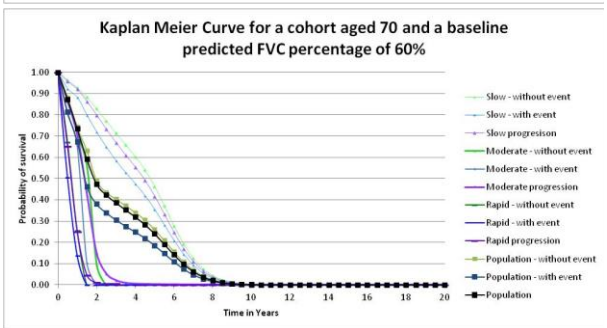

Kaplan Meier Curve for a cohort aged 70 and a baseline predicted FVC percentage of 60%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

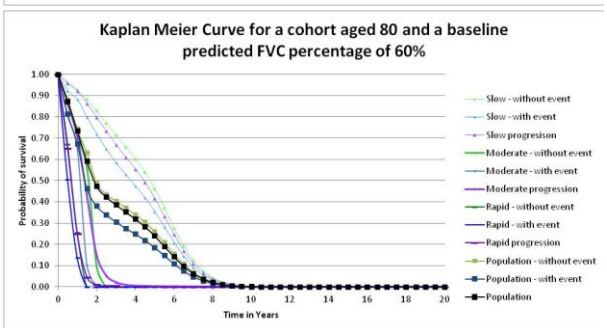

Kaplan Meier Curve for a cohort aged 80 and a baseline predicted FVC percentage of 60%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

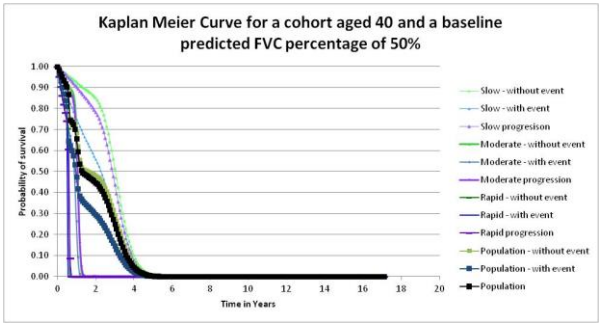

Kaplan Meier Curve for a cohort aged 40 and a baseline predicted FVC percentage of 60%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

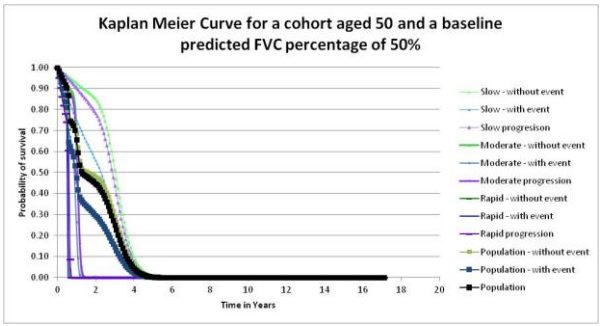

Kaplan Meier Curve for a cohort aged 50 and a baseline predicted FVC percentage of 60%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

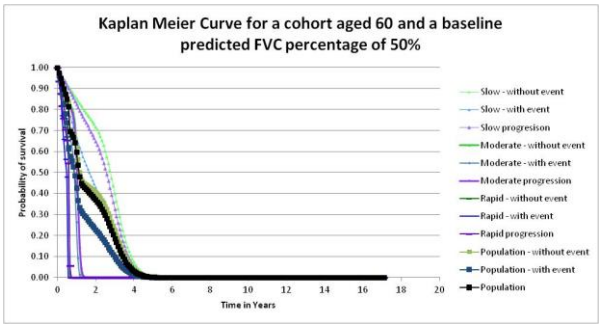

Kaplan Meier Curve for a cohort aged 60 and a baseline predicted FVC percentage of 60%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

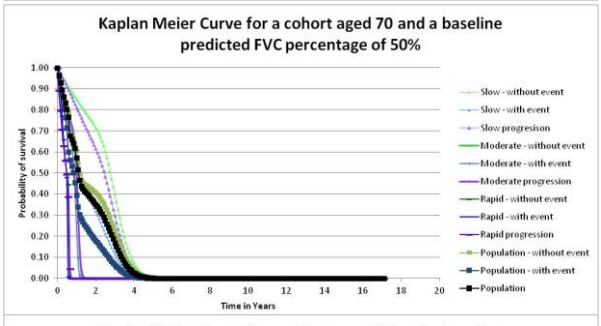

Kaplan Meier Curve for a cohort aged 70 and a baseline predicted FVC percentage of 60%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

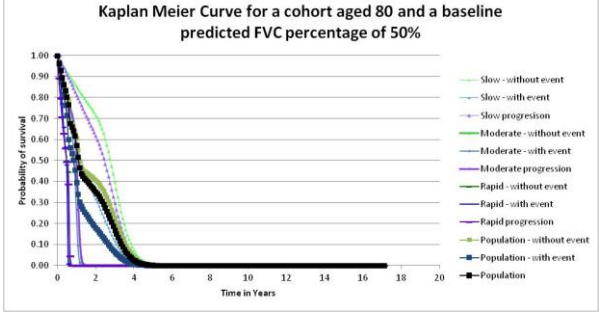

Kaplan Meier Curve for a cohort aged 80 and a baseline predicted FVC percentage of 60%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

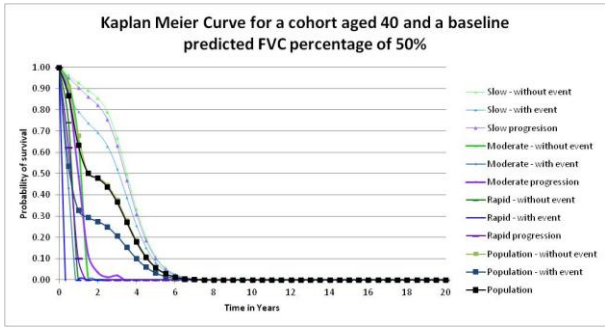

Kaplan Meier Curve for a cohort aged 40 and a baseline predicted FVC percentage of 50%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

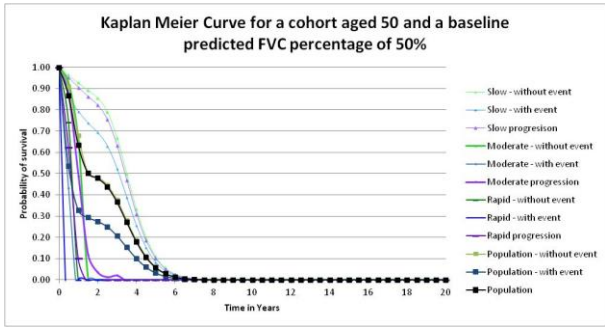

Kaplan Meier Curve for a cohort aged 50 and a baseline predicted FVC percentage of 50%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

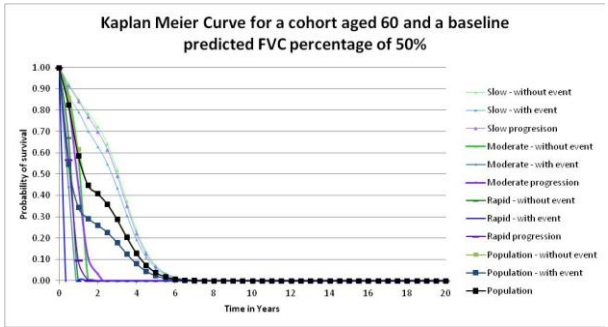

Kaplan Meier Curve for a cohort aged 60 and a baseline predicted FVC percentage of 50%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

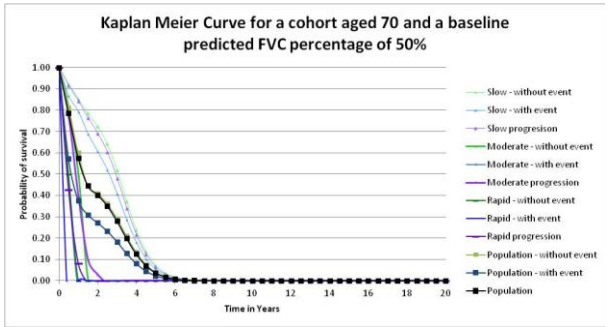

Kaplan Meier Curve for a cohort aged 70 and a baseline predicted FVC percentage of 50%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

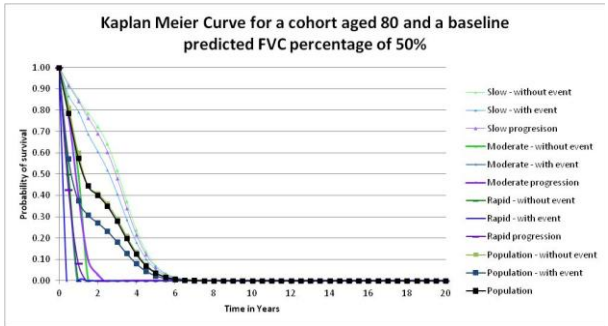

Kaplan Meier Curve for a cohort aged 80 and a baseline predicted FVC percentage of 50%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population


Kaplan Meier Curve for a cohort aged 40 and a baseline predicted FVC percentage of 50%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population


Kaplan Meier Curve for a cohort aged 50 and a baseline predicted FVC percentage of 50%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population


Kaplan Meier Curve for a cohort aged 60 and a baseline predicted FVC percentage of 50%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population


Kaplan Meier Curve for a cohort aged 70 and a baseline predicted FVC percentage of 50%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population


Kaplan Meier Curve for a cohort aged 80 and a baseline predicted FVC percentage of 50%
Probability of survival
Time in Years
Slow - without event
Slow - with event
Slow progresison
Moderate - without event
Moderate - with event
Moderate progression
Rapid - without event
Rapid - with event
Rapid progression
Population - without event
Population - with event
Population

Appendix N: Adverse events table

N.1.1 Adverse events prioritised by GDG

Drug	Priority adverse events
Corticosteroid (prednisolone)	Weight gain Osteoporosis Cataract Diabetes/ hyperglycaemia Skin thinning.
Immunospressant (mycophenolate mofetil)	Bone marrow suppression (infections) Pancytopenia Skin cancer Hepatic dysfunction Malignancy Blood disorders Gastrointestinal
Immunosuppressant (azathioprine)	Bone marrow suppression (infections) Blood disorders Hypersensitivity Liver function abnormalities Vomiting, sudden fevers, myalgia and arthralgia necessitating immediate withdrawal
Anticoagulant (warfarin)	Haemorrhage Hepatic dysfunction Bruising Skin necrosis
Mucolytic (N-acetylcysteine)	Diarrhoea Hepatic dysfunction nausea
Proton pump inhibitor	Gastrointestinal Increased risk of clostridium difficile Fractures Abdominal pain nausea
Antibiotic (co-trimoxazole)	Nausea Bone marrow suppression Allergy/ hypersensitivity Rash Diarrhoea
Endothelial receptor antagonist (ambrisentan)	Allergy/ Hypersensitivity Hepatic dysfunction Anaemia
Endothelial receptor antagonist	Allergy/ hypersensitivity Hepatic dysfunction Blood disorders

Drug	Priority adverse events
(bosentan)	
PDE inhibitor (sildenafil)	Visual impairment Cardiovascular disease Flushing Dry mouth

Appendix O: The cost of pharmacological interventions for IPF

Intervention; with assumed dose/duration of treatment for typical IPF patient [a]	Unit cost of pharmacological intervention [based on drug tariff, March 2013, and unless otherwise stated][351 5]	Additional Costs; monitoring/prevention of complications [b]	Expected cost per patient per year (nearest pound)	Notes
Prednisolone 40 mg daily for first 4 weeks 30 mg daily for weeks 4-8 20mg daily for weeks 8-12 10mg thereafter NB: this dosage differs from that cited in the BNF and was agreed to be typical by clinical members of the GDG	Cost per 5mg 28 tab pack = £0.96 Cost per week For wks 1-4: £1.92 For wks 4-8: £1.44 For wks 8-12: £0.96 For weeks 12+:£0.48 Cost per 1st year = £36.48 Cost per year thereafter = £24.96	Monitoring Assessment for corticosteroid complications, once on initiation and twice per year thereafter as a minimum. Assessment would include screening for contraindications, as well as regular blood pressure and urine testing Vitamin D supplementation may be offered. A Dexa bone scan is sometimes offered to patients considered at risk of osteoporosis. Dexa scan = £77 [107] General practice nurse time per consultation = £10[381] Urine testing: Costs vary depending on how many substances can be detected and on the supplier. Typical price per Clinistix® (and similar) is approximately 5-8 pence per stick. Strips detecting 7 or 10 different substances can cost up to 20 pence per strip. Calcium and Ergocalciferol (10mg) (Calcium and Vitamin D) 28 tab pack costs £7.91. A year of one tablet daily = £143.11 For the costing it is assumed that monitoring occurs via 4 primary care nurse consultation per year and that staff time is the only significant cost. Cost of monitoring + supplements per year + dexa = (4*£10) + £103.11+£77 = £220.11	Cost of drug = £36 (1st year) Additional costs = £220 Total = £256	Alternative drugs in the same class. Betamethasone; cortisone acetate; deflazacort; dexamethasone; hydrocortisone; methylprednisolone; prednisone; triamcinolone

Intervention; with assumed dose/duration of treatment for typical IPF patient [a]	Unit cost of pharmacological intervention [based on drug tariff, March 2013, and unless otherwise stated][351 5]	Additional Costs; monitoring/prevention of complications [b]	Expected cost per patient per year (nearest pound)	Notes
Mycophenolate mofetil 1g twice daily	Cost per 500mg 50-tab pack=£7.11 Cost per day = £0.57 Cost per week = £3.98 Cost per year = £207.04	Monitoring Patients monitored for neutropenia, concomitant medications, viral infections, or some combination of these causes. Complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. Cost of full blood count: £2.49[112] Cost of nurse time per procedure in primary care: £9[381] Assumed number of tests per year: 19 Cost of tests per year: £47.31+£171 =£218.31	Cost of drug = £207 Additional costs = £218 Total = £425	Brands include: Arzip® Cellcept® Myfortic® [NB higher dosage may be required]
Warfarin Dose according to INR Assumed dose of 3mg daily	Cost per 3mg 28-tab pack=£0.78 Cost per day = £0.03 Cost per week = £0.20 Cost per year = £10.14	Monitoring INR be determined daily or on alternate days in early days of treatment, then at longer intervals, 4-6 weeks, then up to every 12 weeks. INR testing may be done by NHS in clinic or primary care. The NHS reference cost takes data from both settings. Estimates from literature Cost per year of INR monitoring = £155[223,223] Cost per year, clinic setting = £98.47 [80,146] Cost per year, primary care setting = £283.10 [345,346] Estimate from NHS reference cost Number of visits per year, assuming daily for first week and monthly thereafter: 7+12 = 19 Anticoagulation clinics [non consultant led – service code 324]: £22 first visit; £10 for each follow-up visit cost per year = £22+£180 = £202[107]	Assuming no adverse event Cost of drug = £10 Additional costs = £202 Total = £210	

Intervention; with assumed dose/duration of treatment for typical IPF patient [a]	Unit cost of pharmacological intervention [based on drug tariff, March 2013, and unless otherwise stated][351 5]	Additional Costs; monitoring/prevention of complications [b]	Expected cost per patient per year (nearest pound)	Notes
Azathioprine 2mg/kg – max 150mg per day Assume 125 mg per day	Cost per 25mg 28-tab pack=£4.41 Cost per 50mg 56 tab-pack = £4.36 Cost per day = £0.31 Cost per week = £2.20 Cost per year = £114	Monitoring Monitor for toxicity throughout treatment (including routine liver tests); monitor full blood count weekly (more frequently with higher doses or if severe hepatic or renal impairment) for first 4 weeks, at least every 3 months. Consider measuring TPMT activity before starting azathioprine Estimated cost of TPMT assay: £20 [price for service quoted by City Hospital, Birmingham][68] Cost of nurse time per procedure in primary care: £9[381] Cost of TPMT = £29 Full Blood Count Cost of full blood count: £2.49[112] Cost of nurse time per procedure in primary care: £9[381] Assumed number of tests per year: 7 Cost of tests per year: £17.43+£63.00 =£80.43 Liver Function Tests Cost of liver function test: £4.12[112] Cost of nurse time per procedure in primary care: £9[381] Assumed number of tests per year: 13 Cost of tests per year: £53.56+£117 =£170.56	Cost of drug = £114 Additional costs (inc TPMT) = £280 Total = £394	Brands include Azamune®, Imuran®
N-acetyl cysteine 600mg 3 times daily	N-acetylcysteine, as an oral agent, is only available as an unlicensed generic. The following is an example	No additional monitoring required	Cost of drug = £158.34 Total = £158	Oral form not licensed in the UK – therefore not quoted in BNF or tariff. Used as adjunctive

Intervention; with assumed dose/duration of treatment for typical IPF patient [a]	Unit cost of pharmacological intervention [based on drug tariff, March 2013, and unless otherwise stated][351 5]	Additional Costs; monitoring/prevention of complications [b]	Expected cost per patient per year (nearest pound)	Notes
	correct of 13/03/2013 Cost per 600 mg 100 tab pack= £14.50 (direct communication with Pharmacarma International Ltd.) Cost per day = £0.44 Cost per week = £3.05 Cost per year = £158.34			therapy to immunosuppressant Other possible suppliers include (prices correct of 2009) [52] : IDIS World Medicines approx. £38 (+VAT) for 60 capsules Mawdsleys Unlicensed approx. £12.50 (+VAT) for 60 capsules Alternatives include: Carbocisteine. A 120 cap pack (375mg) costs £17.57 . Assuming a 1.5g daily dose, a year supply costs £213.
Proton-pump inhibitors – Lansoprazole 15–30 mg daily	Cost per 30mg 28 tab pack = £1.72 Assuming 30mg daily dose Cost per day = £0.06 Cost per week: £0.43 Cost per year = £22.36	No additional monitoring required	Cost of drug = £22.36 Total = £22	
Co-trimoxazole (Septrin®)	Cost per 960mg 100-tab	Monitoring	Cost of drug = £171	Brands include:

Intervention; with assumed dose/duration of treatment for typical IPF patient [a]	Unit cost of pharmacological intervention [based on drug tariff, March 2013, and unless otherwise stated][351 5]	Additional Costs; monitoring/prevention of complications [b]	Expected cost per patient per year (nearest pound)	Notes
960mg given twice daily	pack = £23.46 Cost per day = £0.47 Cost per week = £3.28 Cost per year = £170.79	Monitor blood counts on prolonged treatment Cost of full blood count: £2.49[112] Cost of nurse time per procedure in primary care: £9[381] Assumed number of tests per year: 12 Cost of tests per year: £29.88+£108=£137.88	Additional costs = £138 Total = £309	Fectrim®, Fectrim® Forte
Ambrisentan - Volibris® 5mg given daily	Cost per 5 or 10 mg 30-tab pack = £1,651.07 Cost per day = £55.04 Cost per week = £385.25 Cost per year = £20,032 .98 For treatment using HRG code XD01Z: £215 per unit[107]	Monitoring Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended. Cost of liver function test: £4.12[112] Cost of nurse procedure in primary care: £9[381] Assumed number of tests per year: 13 Cost of tests per year: £53.56+£117 =£170.56 It is recommended that haemoglobin and/or haematocrit levels are measured during treatment e.g. at 1 month, 3 months and periodically thereafter in line with clinical practice. Cost of full blood count: £2.49[112] Cost of nurse procedure in primary care: £9[381] Assumed number of tests per year: 5 Cost of tests per year: £12.45+£45 =£57.45	Cost of drug = £20033 Additional costs = £228 Total = £20261	Excluded from tariff Cost sourced by MIMS Unbundled HCD (OPSC code X821) No non-proprietary form available
Bosanten - Tracleer® Initially 62.5 mg twice daily increased after 4 weeks to 125 mg twice daily; max. 250 mg twice daily	Cost per 62.5 mg 56-tab pack = £1,510.21 [3] Cost per 125mg 56-tab pack = £1,510.21 [3] Cost per day = £26.97	Self-administered Monitoring Liver aminotransferase levels measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Tracleer. In addition, liver	Cost of drug = £19,633 Additional costs = £171 Total = £19,804	Excluded from tariff when used for IPF Cost sourced by MIMS Unbundled HCD (OPSC code X822)

Intervention; with assumed dose/duration of treatment for typical IPF patient [a]	Unit cost of pharmacological intervention [based on drug tariff, March 2013, and unless otherwise stated][351 5]	Additional Costs; monitoring/prevention of complications [b]	Expected cost per patient per year (nearest pound)	Notes
	Cost per week = £377.55 Cost per year = £19,632.73 For treatment using HRG code XD02Z: £1,191 per unit[107]	aminotransferase levels measured 2 weeks after any dose increase. Cost of liver function test: £4.12[112] Cost of nurse procedure in primary care: £9[381] Assumed number of tests per year: 13 Cost of tests per year: £53.56+£45=£57.45		No non-proprietary form available
Sildenafil - Revatio® By mouth, 20 mg 3 times daily;	Cost per 20mg 90 tab pack = £373.50 [3] Cost per day = £12.45 Cost per week = £87.15 Cost per year = £4531.80 For treatment using HRG code XD01Z: £215 per unit[107]	Self-administered. No additional monitoring required.	Cost of drug = £4532 Total= £4,532	Excluded from tariff when used for IPF Cost sourced by MIMS Unbundled HCD (OPSC code X821) No non-proprietary form available

Abbreviations: INR = International normalized ratio; ACC = anticoagulation clinic care; TPMT = thiopurine methyltransferase. HRG = Health Resource Group; HCD = High Cost Drug.

(a) Pharmacological Intervention:

- *a. Dose: Unless otherwise stated, these dosages are as per the BNF 2011 and validated by clinical members of the GDG for appropriateness to the IPF population.. Consideration given to whether given daily, twice daily etc.*
- *b. Duration of course: course for all interventions assumed to last as long as treatment is effective*

(b) Additional Costs:

- *a. Route of administration: all interventions are self-administered.*
- *b. Therapeutic Drug Monitoring: for example INR testing, plasma concentration monitoring, and biochemical assay. Frequency and setting this is conducted is noted with estimate of cost.*
- *c. Consideration given to common or severe side effects that have an impact on health/resource use: any preventative measures taken (noting dose etc.), likely resource impact of adverse event (i.e. emergency admission for acute GI bleed) etc.*

Appendix P: Research recommendations

P.1 The value of bronchoalveolar lavage

Research question:

What is the value of bronchoalveolar lavage in people in whom idiopathic pulmonary fibrosis is considered the most likely diagnosis when clinical and computed tomography findings are insufficient to support a confident diagnosis?

Why this is important: A confident diagnosis of idiopathic pulmonary fibrosis needs integration of clinical and computed tomography findings in a multidisciplinary setting. However, a consensus diagnosis cannot always be made with confidence. In some people with 'probable idiopathic pulmonary fibrosis', bronchoalveolar lavage alone may help attain a more confident diagnosis while in others, a subsequent surgical lung biopsy may be needed. It is not known whether the benefits of attaining a more confident diagnosis by bronchoalveolar lavage outweigh the risks of the procedure. A randomised controlled trial should be conducted to determine the potential benefits and risks of bronchoalveolar lavage with regard to increasing diagnostic certainty and avoiding the need for surgical lung biopsy. The study should incorporate outcomes that include diagnostic certainty (sensitivity, specificity), mortality (all-cause and idiopathic pulmonary fibrosis-related), health-related quality of life and change in lung function. Adjustments should be made for differences in baseline clinical and radiological features. Clinical studies should be of sufficient power and duration and include a health economic evaluation

Criteria for selecting high-priority research recommendations:

PICO question	What is the value of bronchoalveolar lavage in patients in patients in whom IPF is suspected clinically, but the CT findings are insufficient to support a confident diagnosis?
Importance to patients or the population	Results would inform recommendations for, or against routine BAL when diagnosing people with IPF
Relevance to NICE guidance	Future NICE guidance may recommend BAL as a first line option before SLB.
Relevance to the NHS	If outcomes are positive (high sensitivity and specificity), then BAL may prove to increase diagnostic certainty for people with IPF. BAL analysis may not be routinely available in all secondary care centres and will require additional resource
National priorities	None
Current evidence base	There are no suitable studies addressing this.
Equality	The research question has no particular equality issues.
Study design	A controlled trial should be conducted to determine the potential benefits and risks of BAL in adults.
Feasibility	There are specialist secondary care facilities which offer BAL and its analysis routinely, so there will be an adequate infrastructure for a study.
Other comments	None
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

P.2 The value of surgical lung biopsy

Research question:

What is the value of surgical lung biopsy in people in whom idiopathic pulmonary fibrosis is considered the most likely diagnosis when clinical and computed tomography findings are insufficient to support a confident diagnosis?

Why this is important: A confident diagnosis of idiopathic pulmonary fibrosis needs integration of clinical and computed tomography findings in a multidisciplinary setting. However, a consensus diagnosis cannot always be made with confidence. In such cases of 'probable idiopathic pulmonary fibrosis', surgical lung biopsy may be indicated to allow a diagnosis to be made with greater confidence. It is not known whether the benefits of attaining a more confident diagnosis outweigh the risks of surgical lung biopsy. A randomised controlled trial should be conducted to determine the potential benefits and risks of biopsy with regard to diagnostic certainty (sensitivity, specificity), mortality (all-cause and idiopathic pulmonary fibrosis-related), health-related quality of life and change in lung function. Adjustments should be made for differences in baseline clinical and radiological features. Clinical studies should be of sufficient power and duration and include a health economic evaluation.

Criteria for selecting high-priority research recommendations:

PICO question	What is the value of surgical lung biopsy in patients in whom IPF is suspected clinically, but the CT findings are insufficient to support a confident diagnosis?
Importance to patients or the population	Results would inform recommendations for, or against the value of surgical lung biopsy when diagnosing people with IPF.
Relevance to NICE guidance	Future NICE guidance would be able to specify criteria for when a SLB may be appropriate.
Relevance to the NHS	Surgical lung biopsy requires significant resource. The outcome of a study may increase or reduce the SLB rate
National priorities	None
Current evidence base	There are no suitable studies addressing this.
Equality	The research question has no particular equality issues.
Study design	A controlled trial should be conducted to determine the potential benefits and risks of SLB in adults.
Feasibility	Surgical lung biopsy is performed in selected centres only, but the service is available to all secondary care sites.
Other comments	None
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

P.3 P.3 The value of transthoracic echocardiography

Research question:

What is the value of transthoracic echocardiography in detecting pulmonary hypertension and determining prognosis in people with idiopathic pulmonary fibrosis?

Why this is important: People with IPF sometimes develop pulmonary hypertension. This may be an indicator of poor prognosis. Pulmonary artery pressure (PAP) can only be accurately measured by right heart catheter which is an invasive procedure. Transthoracic doppler echocardiography (TCC) is a non-invasive technique for estimating PAP although values correlate poorly with those obtained by right heart catheterisation. The benefits of estimating PAP in people with IPF, at the time of diagnosis or serially thereafter, is not known. A study should be undertaken to determine whether estimation of PAP is a useful predictor of prognosis for disease progression in IPF. The study should address the additive value of TCC over other routinely performed tests, by measuring rates of survival, mortality (all-cause and IPF-related); hospitalisation (all-cause, non-elective and IPF-related); change in lung function (vital capacity and diffusion capacity for carbon monoxide); 6 minute walk distance; breathlessness score; health related quality of life measures (ideally employing a tool validated in IPF patients); and development of pulmonary hypertension as measured by right heart catheterisation. Clinical studies should be of sufficient power and duration and include health economic evaluation.

Criteria for selecting high-priority research recommendations:

PICO question	What is the value of transthoracic echocardiography (TCC) in detecting pulmonary hypertension and determining prognosis in people with IPF?
Importance to patients or the population	People with IPF may present with co-existing pulmonary hypertension, or may develop pulmonary hypertension over time. Several studies have suggested that pulmonary hypertension is a poor prognostic indicator in IPF.
Relevance to NICE guidance	Future NICE guidance may recommend routine TCC in order to predict prognosis in people with IPF.
Relevance to the NHS	TCC is widely available but requires resource. Most centres do not perform TTC routinely in all patients with IPF.
National priorities	None.
Current evidence base	The NICE IPF guideline development systematic review found no adequate evidence to support or condemn the use of transthoracic echocardiography. No research has been done to modern standards.
Equality	The research question has no particular equality issues.
Study design	Cohort studies investigating the prognostic value of TCC in adults should be adequately powered and measure mortality/ survival (time to event data).
Feasibility	TCC is available in most secondary care centres.
Other comments	None.
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

P.4 Agreement between radiologists in the interpretation of CT

Research question:

What is the agreement between radiologists in the interpretation of CT in patients with suspected idiopathic pulmonary fibrosis?

Why this is important: Interpretation of the computed tomography (CT) is of pivotal importance in the diagnosis of IPF. Patients with a consistent clinical history can be confidently diagnosed with IPF if the CT is considered indicative of the usual interstitial pneumonia (UIP) pattern of disease. Previous studies from North America have attempted to determine the agreement between radiologists in interpreting CT images in patients with suspected IPF, but these predated the most recently published international consensus criteria for the diagnosis of IPF and these previous studies may not reflect current practice in the UK. A multicentre study should be performed to determine the level of agreement between radiologists of varying expertise for the diagnosis of UIP pattern of disease on CT. Clinical studies should be of sufficient power and duration, and should routinely include health economic evaluation.

Criteria for selecting high-priority research recommendations:

PICO question	What is the agreement between radiologists in the interpretation of CT in patients with suspected IPF?
Importance to patients or the population	CT appearances are pivotal in the diagnosis of IPF. Uniformity of CT interpretation would ensure that IPF is diagnosed appropriately and accurately.
Relevance to NICE guidance	None.
Relevance to the NHS	It is not known if there is adequate expertise in CT interpretation in all secondary care centres. Expert chest CT interpretation requires resource.
National priorities	None.
Current evidence base	The NICE IPF guideline development systematic review found no adequate evidence to support or condemn the use of computed tomography. No research has been done to modern standards.
Equality	The research question has no particular equality issues.
Study design	A multicentre study should determine the level of agreement between radiologists when assessing the diagnosis of UIP pattern of disease.
Feasibility	CT scans are digitally archived and can be independently reviewed
Other comments	None.
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

P.5 CT scoring systems

Research question:
What is the feasibility of a formal 'CT scoring system' to assess disease severity in patients with suspected idiopathic pulmonary fibrosis?

Why this is important: There are a number of published 'CT scoring systems' that have been validated to varying extents. Scoring of CT consumes resources. There is no data comparing different CT scoring systems in terms of inter- and intra-observer agreement, functional correlation and ease of use. There are no data comparing observers at MDTs in secondary and tertiary care for inter- and intra-observer agreement of CT scoring. Studies should be performed that compare different CT

scoring systems in terms of ease of use, observer agreement and correlation with functional indices. Clinical studies should be of sufficiently long duration, sufficiently powered and should include health economic evaluation.

Criteria for selecting high-priority research recommendations:

PICO question	What is the feasibility of a formal 'CT scoring system' to assess disease severity in patients with suspected IPF?
Importance to patients or the population	There are a number of CT scoring systems used for research purposes but the applicability in clinical practice is not known
Relevance to NICE guidance	Future NICE guidance may include formal CT scoring or quantification if it is found to be valuable in determining disease severity
Relevance to the NHS	Formal CT scoring is routinely performed and requires resource
National priorities	None
Current evidence base	The NICE IPF guideline development systematic review found no adequate evidence to support or condemn the use of computed tomography scoring. No research has been done to modern standards.
Equality	The research question has no particular equality issues.
Study design	A blinded study of independently scored CT scans
Feasibility	CT scans are digitally archived and can be independently reviewed
Other comments	None
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

P.6 Utility of a formal CT scoring system in determining outcomes

Research question:
What is the utility of a formal CT scoring system in determining outcome in patients with suspected idiopathic pulmonary fibrosis?

Why this is important: Some evidence suggests that composite score systems (including CT scoring) are of value in predicting prognosis in IPF. There is little information on whether a score suggesting CT abnormalities at the time of diagnosis or whether scoring a change in CT appearance at follow-up might independently predict prognosis. Studies should be undertaken to compare different CT scoring systems in patients with IPF evaluating the extent, pattern and ancillary features of fibrosis (including any co-existing conditions such as emphysema) at diagnosis. Furthermore, longitudinal observational studies should measure inter-observer agreement comparing observers with different levels of expertise at multi-disciplinary teams (MDTs) of secondary and tertiary care level. Primary outcomes should include a correlation between CT scores and survival. Study length should be 5 years and also be sufficiently powered and include health economic evaluation.

Criteria for selecting high-priority research recommendations:

PICO question	What is the utility of a formal CT scoring system in determining outcome

	in patients with suspected IPF?
Importance to patients or the population	Severity of disease in IPF is generally assessed by symptoms and lung function testing. The value of quantifying CT abnormalities by CT scoring in predicting outcome, or for monitoring disease progression is not known
Relevance to NICE guidance	Future NICE guidance may include formal CT scoring or quantification if it is found to be valuable in determining disease progression
Relevance to the NHS	Formal CT scoring is routinely performed and requires resource
National priorities	None
Current evidence base	The NICE IPF guideline development systematic review found no adequate evidence to support or condemn the use of computed tomography scoring systems. No research has been done to modern standards.
Equality	The research question has no particular equality issues.
Study design	Longitudinal observational studies should measure CT scores against disease progression. Primary outcomes should include association between CT scores and survival. Adjustments should be made for variables known to predict outcome in IPF.
Feasibility	CT scans are digitally archived and can be independently reviewed
Other comments	None
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

P.7 Pulmonary rehabilitation

Research question:
Does pulmonary rehabilitation improve outcomes for patients with idiopathic pulmonary fibrosis?

Why this is important: There is evidence that patients with idiopathic pulmonary fibrosis may benefit from pulmonary rehabilitation. However this evidence is mostly derived from programmes designed principally for patients with chronic obstructive pulmonary disease. It is likely that the needs of people with idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease differ. Randomised controlled trials should be carried out to determine the effects of pulmonary rehabilitation programmes tailored to idiopathic pulmonary fibrosis, compared with currently offered pulmonary rehabilitation programmes, on quality of life, walking distance and lung function with analysis adjusting for confounding factors appropriately. Trials should analyse benefits of the different aspects of pulmonary rehabilitation including the components, setting and location of the programme, and healthcare resources involved. End points may include: 6-minute walk distance; breathlessness score; a measure of health-related quality of life (ideally employing a tool validated in people with idiopathic pulmonary fibrosis): mortality (all-cause and idiopathic pulmonary fibrosis-related); hospitalisation (all-cause, non-elective and idiopathic pulmonary fibrosis -related); lung function (vital capacity and diffusion capacity for carbon monoxide). Studies should be of sufficient power and duration and include a health economic evaluation.

Criteria for selecting high-priority research recommendations:

PICO question	Does pulmonary rehabilitation improve outcomes for patients with IPF?
Importance to patients or the population	Pulmonary rehabilitation may consist of various exercise or educational components Currently, patients with IPF are most likely to be offered pulmonary rehabilitation tailored to people with COPD, if at all.
Relevance to NICE guidance	Future NICE guidance may be able to specify components of pulmonary rehabilitation programmes which are proven to improve quality or life outcomes specifically for people with IPF.
Relevance to the NHS	Pulmonary rehabilitation specifically designed for IPF would have resource implications
National priorities	None
Current evidence base	There are no suitable studies addressing the components of pulmonary rehabilitation programmes in people with IPF.
Equality	The availability, setting and locations of pulmonary rehabilitation programmes should be tailored to all people with IPF, including those with disabilities.
Study design	Controlled trials should investigate the benefit of pulmonary rehabilitation components in adults, be adequately powered and measure patient centred outcomes.
Feasibility	Pulmonary rehabilitation facilities are widely available.
Other comments	None
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

P.8 Nocturnal oxygen

Research question:

Does nocturnal oxygen improve outcomes in idiopathic pulmonary fibrosis?

Why this is important: Oxygen desaturation during sleep is known to occur in many patients with IPF even if they do not desaturate on exercise. The detection of nocturnal hypoxaemia and its treatment with supplemental oxygen is not currently part of routine clinical practice. A randomised control trial should establish the benefits of supplementary nocturnal oxygen therapy in patients with IPF who develop hypoxia during sleep and include a placebo arm. Endpoints in phase 3 clinical trials in IPF should reflect patient survival, quality of life and functional status. Appropriate endpoints may include 6 minute walk distance; transthoracic echocardiogram to estimate pulmonary artery pressure; breathlessness score; a measure of health related quality of life (ideally employing a tool validated in IPF patients), mortality (all-cause and IPF-related); hospitalisation (all-cause, non-elective and IPF-related). Phase 3 trials should have a duration of greater than 12 months and include health economic evaluation.

Criteria for selecting high-priority research recommendations:

PICO question	Does nocturnal oxygen improve outcomes in IPF?
Importance to patients or the population	Oxygen desaturation during sleep is known to occur in many patients with IPF even if they do not desaturate on exercise. The significance of this is not known

Relevance to NICE guidance	NICE would provide guidance on nocturnal oxygen
Relevance to the NHS	Nocturnal oxygen therapy requires resource
National priorities	None
Current evidence base	There are no suitable studies addressing this.
Equality	The research question has no particular equality issues.
Study design	A randomised control trial should establish the benefits of supplementary nocturnal oxygen therapy versus placebo.
Feasibility	Oxygen therapy is readily available
Other comments	None
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

P.9 Ambulatory oxygen

Research question:
Does ambulatory oxygen improve outcomes in idiopathic pulmonary fibrosis?

Why this is important: People with idiopathic pulmonary fibrosis frequently demonstrate a fall in oxygen saturation during exercise even though they are not hypoxic at rest. In such people, ambulatory oxygen is often provided to improve exercise capacity, enhance mobility and enable activities of daily living in order to improve quality of life. However, there are no randomised controlled trials to demonstrate that ambulatory oxygen therapy is effective in achieving these aims in patients with idiopathic pulmonary fibrosis. A randomised controlled trial should be conducted to determine the effects of ambulatory oxygen on quality of life in people with idiopathic pulmonary fibrosis and consideration given to the use of a placebo arm. This should include a standardised protocol for assessing exercise such as the 6-minute walk test. The end points may include 6-minute walk distance; breathlessness score; a measure of health-related quality of life (ideally employing a tool validated in idiopathic pulmonary fibrosis patients). Phase III trials should have a duration of greater than 12 months and include a health economic evaluation.

Criteria for selecting high-priority research recommendations:

PICO question	Does ambulatory oxygen improve outcomes in IPF?
Importance to patients or the population	Patients with IPF frequently demonstrate a fall in oxygen saturation during exercise even though they are not hypoxia at rest. Ambulatory oxygen is often prescribed to patients that desaturate on exercise, but its value is not known
Relevance to NICE guidance	NICE would recommend ambulatory oxygen if future guidelines
Relevance to the NHS	Ambulatory oxygen requires resource
National priorities	None
Current evidence base	There are no suitable studies addressing this.

Equality	The research question has no particular equality issues.
Study design	A RCT of ambulatory oxygen.
Feasibility	Ambulatory oxygen is readily available. Careful consideration should be given to the use of placebo
Other comments	None
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

P.10 Short burst oxygen therapy

Research question:
Does short-burst oxygen therapy improve outcomes in idiopathic pulmonary fibrosis?

Why this is important: Short-burst oxygen therapy is often used to relieve the symptom of breathlessness on exertion in patients with IPF. However, there is currently no evidence to prove it is effective. The benefit of short-burst oxygen therapy to relieve breathlessness and improve quality of life in patients with IPF should be tested in a randomised control trial. The endpoints must be clinically meaningful and reflect quality of life and functional status. Appropriate endpoints may include, but should not be restricted to; 6 minute walk distance; breathlessness score; a measure of health related quality of life (ideally employing a tool validated in IPF patients, and hospitalisation (all-cause, non-elective and IPF-related). A short-term, cross-over design may be appropriate in this type of intervention. Careful consideration should be given to the use of a placebo arm. Health economic evaluation should be included within the study design.

Criteria for selecting high-priority research recommendations:

PICO question	Does short-burst oxygen therapy improve outcomes in IPF?
Importance to patients or the population	Short-burst oxygen therapy is often used to relieve the symptom of breathlessness on exertion in patients with IPF. However its value is not known
Relevance to NICE guidance	NICE would make recommendations on short burst oxygen therapy
Relevance to the NHS	Short-burst oxygen therapy requires reource
National priorities	None
Current evidence base	There are no suitable studies addressing this.
Equality	The research question has no particular equality issues.
Study design	A short-term cross-over study of oxygen therapy versus placebo
Feasibility	Careful consideration should be given to the use of placebo in this setting
Other comments	None
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

P.11 Pharmacological treatments of cough

Research question:
What is the value of pharmacological treatments of cough in idiopathic pulmonary fibrosis?

Why is it important: At least 70% of people with IPF complain of cough which may impair their quality of life. There is preliminary evidence that pharmacological therapies may be of benefit in controlling the cough associated with IPF. Randomised, placebo-controlled trials of adequate power and duration should be undertaken to determine the benefits, side-effects and appropriate dose of anti-tussive therapies in people with a confirmed diagnosis of IPF who complain of troublesome cough. Studies should incorporate a validated, specific cough questionnaire such as the Leicester Cough Questionnaire (LCQ), a Visual Analogue Score of cough (VAS), an assessment of quality of life such as EQ5D Questionnaire and a health economic assessment. Groups should be matched for confounding variables which can cause cough such as gastro-oesophageal reflux and medication with angiotensin converting enzyme inhibitors. An objective measure of cough, using a 24 hour cough recording, on a small sub-group of patients to support findings on subjective assessments, should also be determined.

Criteria for selecting high-priority research recommendations:

PICO question	What is the value of pharmacological treatments of cough in idiopathic pulmonary fibrosis?
Importance to patients or the population	At least 70% of people with IPF complain of cough which may impair their quality of life, and commonly used therapies are often ineffective
Relevance to NICE guidance	NICE would make recommendations on the management of cough in IPF
Relevance to the NHS	Interventions for cough may require resource
National priorities	None
Current evidence base	There are few studies of novel pharmacological therapies for cough in IPF
Equality	The research question has no particular equality issues.
Study design	Randomised, placebo-controlled trials of adequate power and duration should be undertaken to determine the benefits, side-effects and appropriate dose of anti-tussive therapies in people with a confirmed diagnosis of IPF who complain of troublesome cough.
Feasibility	Dependent upon specific intervention.
Other comments	None
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

P.12 Anti-reflux therapy

Research question:
Is anti-reflux therapy an effective treatment for idiopathic pulmonary fibrosis?

Why this is important: There is evidence from observational studies, and uncontrolled interventional trials, that microaspiration of gastric/oesophageal contents contribute to disease progression, and perhaps even cause idiopathic pulmonary fibrosis. There have been no randomised controlled trials of anti-reflux therapy in idiopathic pulmonary fibrosis but proton-pump inhibitors are often prescribed for symptoms of acid-reflux. A randomised, placebo-controlled trial of adequate power and duration of greater than 12 months should be undertaken to determine the benefits and side effects of anti-reflux therapy, including proton pump inhibition in people with a confirmed diagnosis of idiopathic pulmonary fibrosis. Appropriate end points may include mortality (all-cause and idiopathic pulmonary fibrosis-related); hospitalisation (all-cause, non-elective and idiopathic pulmonary fibrosis-related); lung function (vital capacity and diffusion capacity for carbon monoxide); 6-minute walk distance; breathlessness score; a measure of health-related quality of life (ideally employing a tool validated in idiopathic pulmonary fibrosis patients). Phase III trials should include a health economic evaluation.

Criteria for selecting high-priority research recommendations:

PICO question	Is anti-reflux therapy an effective treatment for IPF?
Importance to patients or the population	There is evidence from observational studies, and uncontrolled interventional trials, that microaspiration of gastric/oesophageal contents contribute to disease progression, and perhaps even cause IPF.
Relevance to NICE guidance	NICE would provide guidance on the value of reflux therapy in IPF
Relevance to the NHS	Anti-reflux therapies may require resource
National priorities	None
Current evidence base	There are no suitable studies to address this
Equality	The research question has no particular equality issues.
Study design	A randomised, placebo-controlled trial of adequate power and duration should be undertaken to determine the benefits and side-effects of anti-reflux therapy, including proton pump inhibition in people with a confirmed diagnosis of IPF
Feasibility	Dependent upon specific anti-reflux strategy
Other comments	None
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

P.13 Corticosteriod therapy

Research question:
Is corticosteroid therapy an effective treatment for IPF?

Why this is important: Historically, high dose oral corticosteroids (≥60mg daily) were used to treat IPF. However, there is recent evidence to suggest that the combination of prednisolone and azathioprine may be harmful and lead to increased mortality. There have been no placebo-controlled trials of corticosteroids as monotherapy in IPF. A randomised, placebo-controlled trial of adequate

power and duration should be undertaken to determine the benefits and side-effects of prednisolone to treat people with IPF. Since high doses of corticosteroids may be harmful, careful consideration should be given to the most appropriate dose to employ. Endpoints in phase 3 clinical trials must reflect patient survival, quality of life and functional status. Appropriate endpoints may include mortality (all-cause and IPF-related); hospitalisation (all-cause, non-elective and IPF-related); lung function (vital capacity and diffusion capacity for carbon monoxide); 6 minute walk distance; and a measure of health related quality of life (ideally employing a tool validated in IPF patients). Phase 3 trials should have a duration of greater than 12 months and include a health economic evaluation.

Criteria for selecting high-priority research recommendations:

PICO question	Is corticosteroid therapy an effective treatment for IPF?
Importance to patients or the population	Historically, high dose oral corticosteroids (≥60mg daily) were used to treat IPF. However, there is recent evidence to suggest that the combination of prednisolone and azathioprine may be harmful and lead to increased mortality. There have been no placebo-controlled trials of corticosteroids as monotherapy in IPF
Relevance to NICE guidance	NICE may recommend corticosteroids for IPF if found to be valuable
Relevance to the NHS	Corticosteroids usage is likely to require resource
National priorities	None
Current evidence base	There are no suitable studies to address this
Equality	The research question has no particular equality issues.
Study design	A randomised, placebo-controlled trial of adequate power and duration should be undertaken to determine the benefits and side-effects of prednisolone to treat people with IPF.
Feasibility	The study is feasible
Other comments	None
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

P.14 Co-trimoxazole

Research question:
Is co-trimoxazole an effective treatment for IPF?

Why this is important: Co-trimoxazole is an antibiotic that may also have immunomodulatory function. In a randomised placebo-controlled trial, treatment with co-trimoxazole did not affect the primary end-point, and change in forced vital capacity over 12 months. The majority of participants had IPF, but some had other idiopathic fibrotic lung diseases. Over one third of participants were taking azathioprine and/or prednisolone. In the subgroup of participants who completed the study as per protocol, co-trimoxazole therapy was associated with fewer deaths. A randomised, placebo-controlled trial should be undertaken to determine if co-trimoxazole therapy reduces mortality in

IPF. The primary endpoint should include all-cause mortality. The comparator should be current best supportive care that does not include the routine use of immunosuppressive drugs including prednisolone. The trial should have a duration of at least 12 months and include a health economic evaluation.

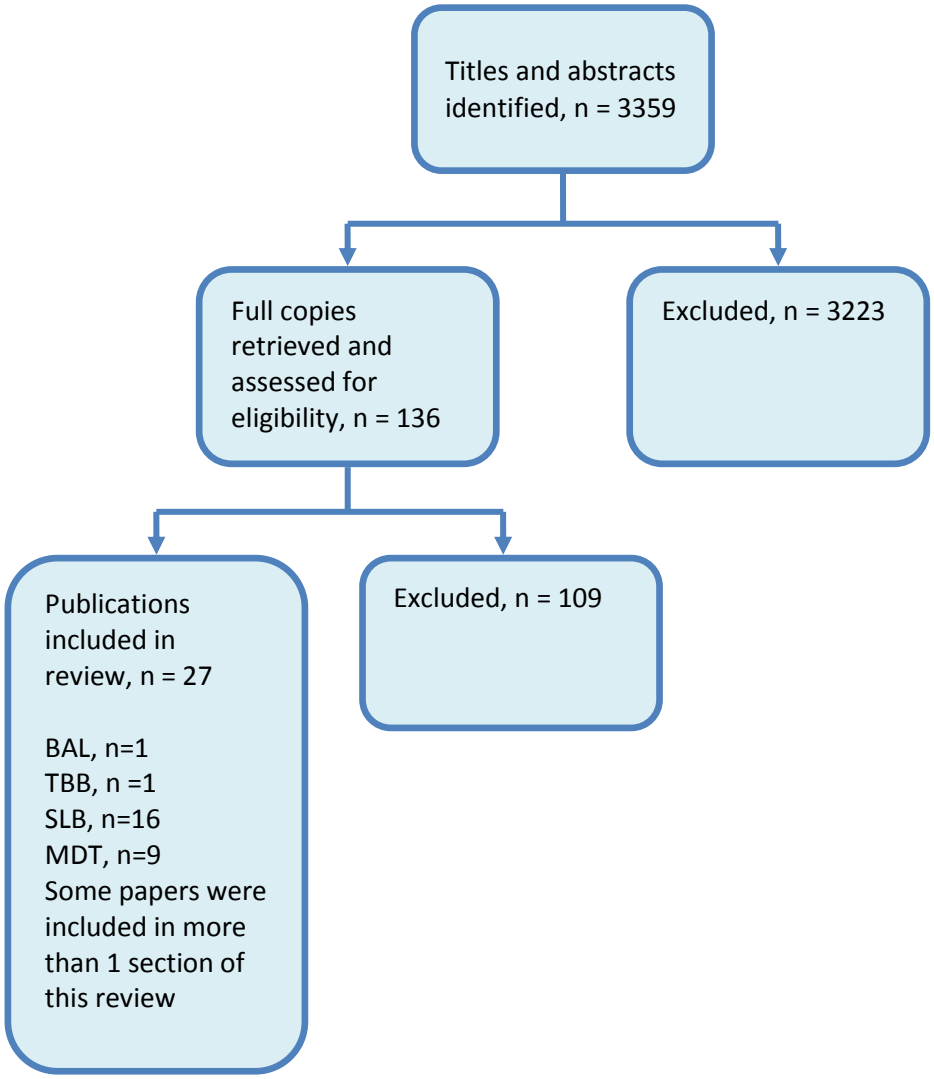
Criteria for selecting high-priority research recommendations:

PICO question	Is co-trimoxazole an effective treatment for IPF?
Importance to patients or the population	Co-trimoxazole is an antibiotic that may also have immunomodulatory function. In one recent randomised placebo-controlled trial, the subgroup of participants who completed the study as per protocol, co-trimoxazole therapy was associated with fewer deaths.
Relevance to NICE guidance	NICE may recommend co-trimoxazole for IPF if found to be valuable.
Relevance to the NHS	Co-trimoxazole usage is likely to require resource.
National priorities	None.
Current evidence base	There are no suitable studies to address this.
Equality	The research question has no particular equality issues.
Study design	A randomised, placebo-controlled trial of adequate power and duration should be undertaken to determine the benefits and side-effects of co-trimxazole to treat people with IPF.
Feasibility	This study is feasible.
Other comments	None.
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

Appendix Q: Adapted Prisma Diagrams

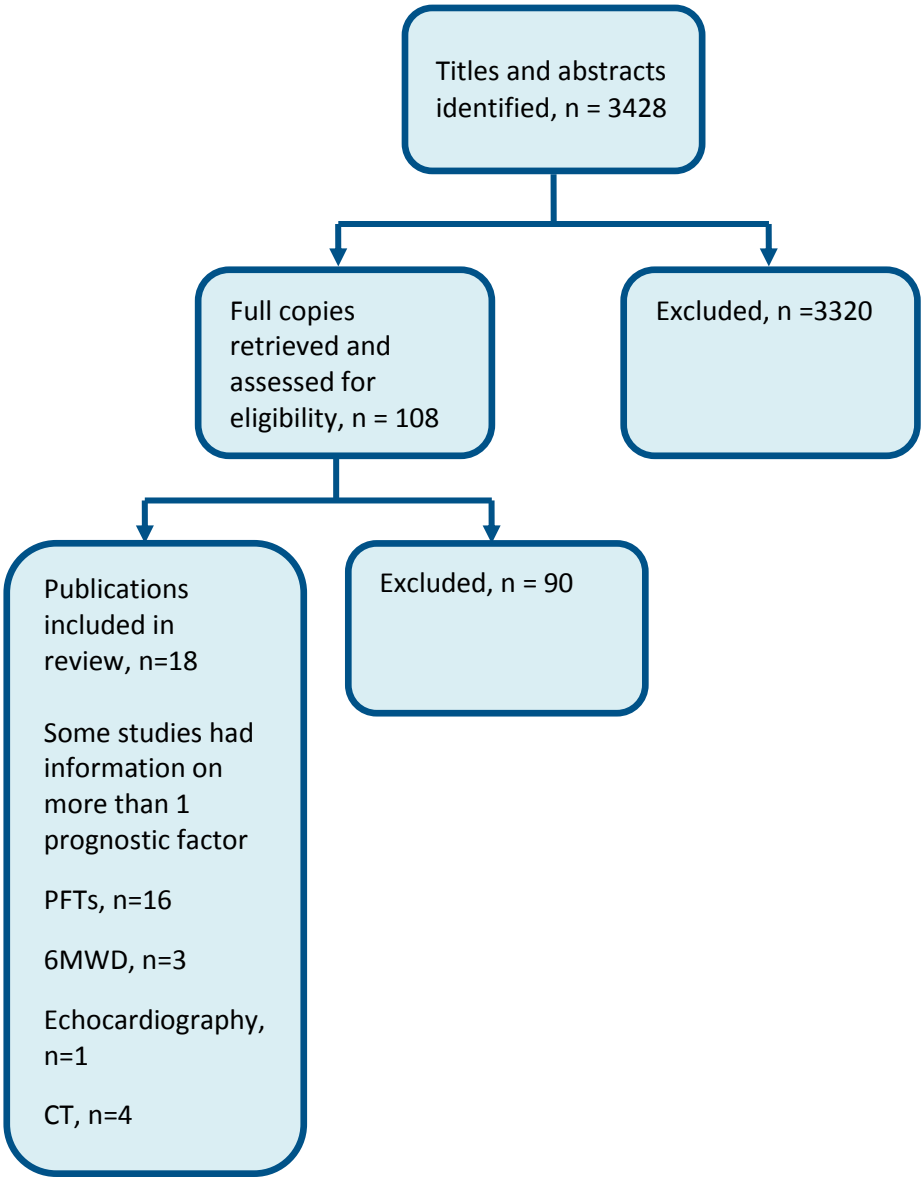
Q.1 Diagnosis

Figure 126: Flow diagram of clinical article selection for diagnostic review (BAL, Biopsy and MDT)



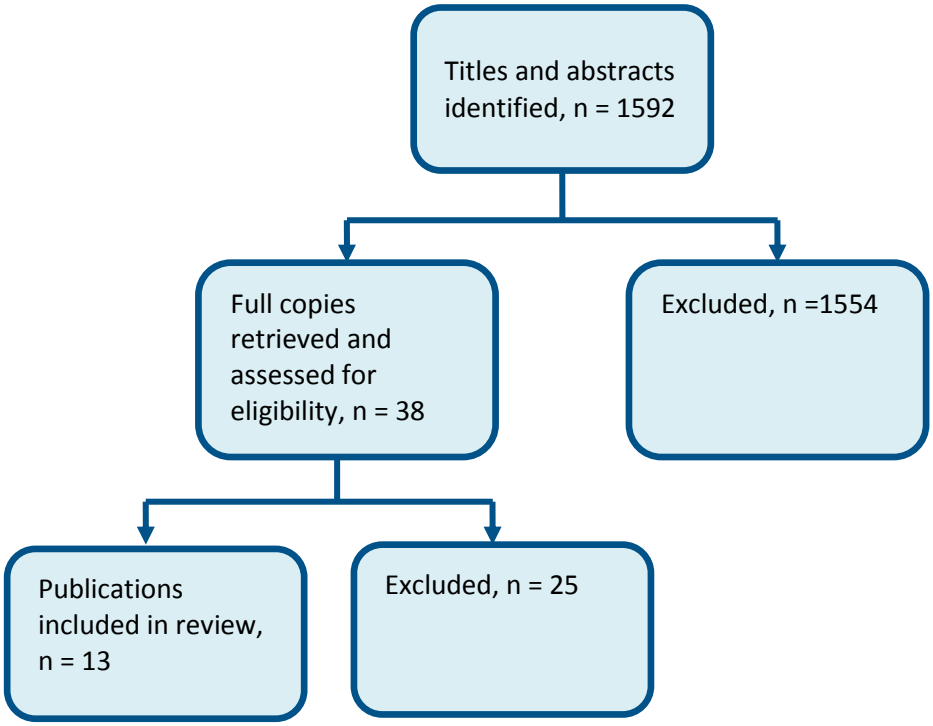
Q.2 Prognosis

Figure 127: Flow diagram of clinical article selection for prognosis review



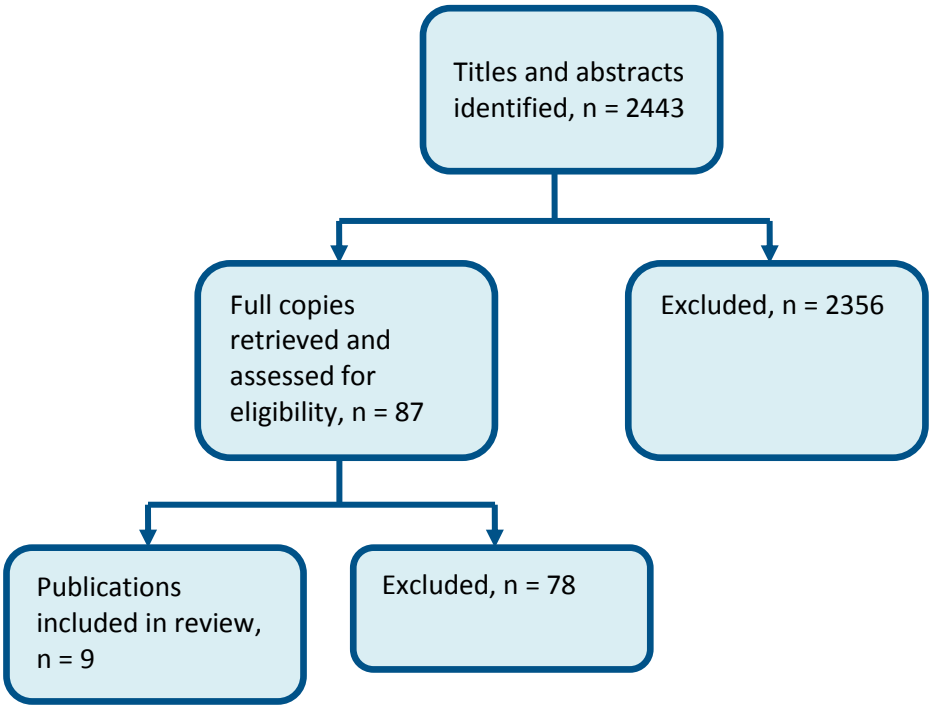
Q.3 Pulmonary rehabilitation

Figure 128: Flow diagram of clinical article selection for pulmonary rehabilitation review



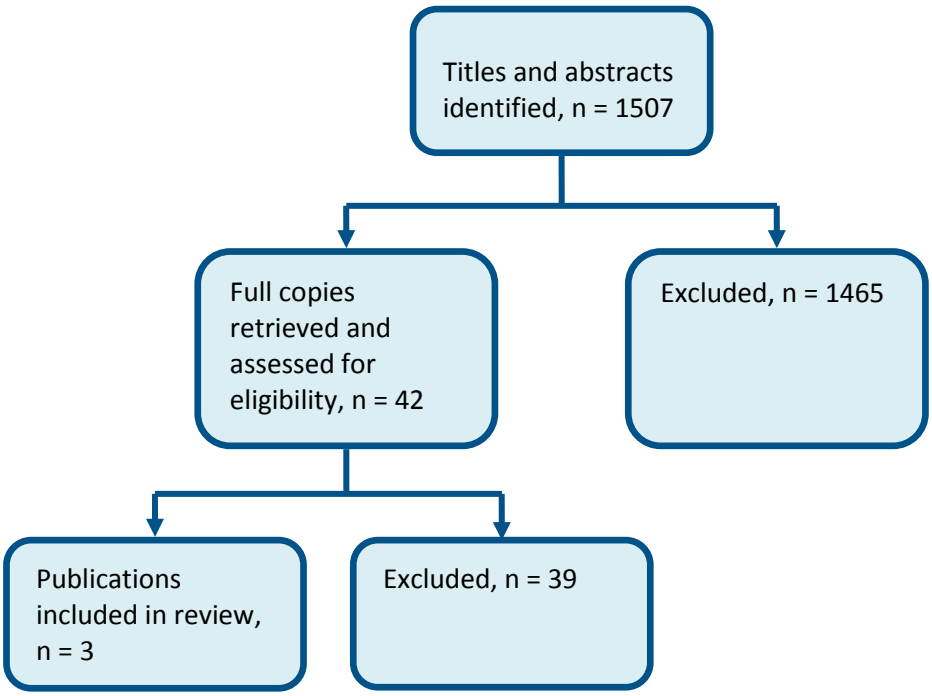
Q.4 Best supportive care

Figure 129: Flow diagram of clinical article selection for best supportive care



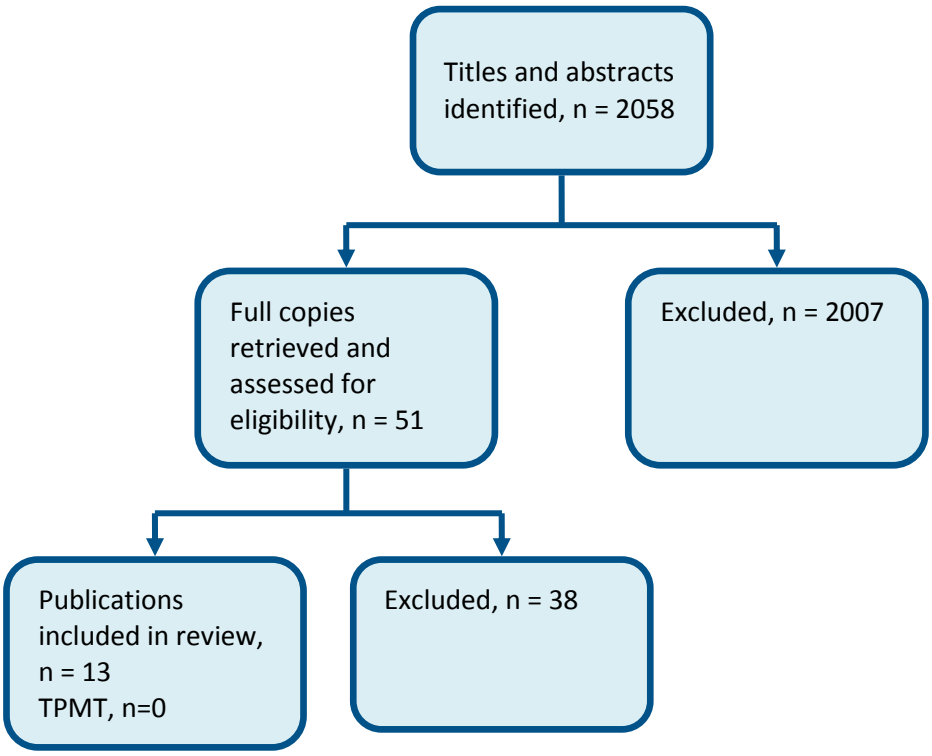
Q.5 Psychosocial support

Figure 130: Flow diagram of clinical article selection for psychosocial support



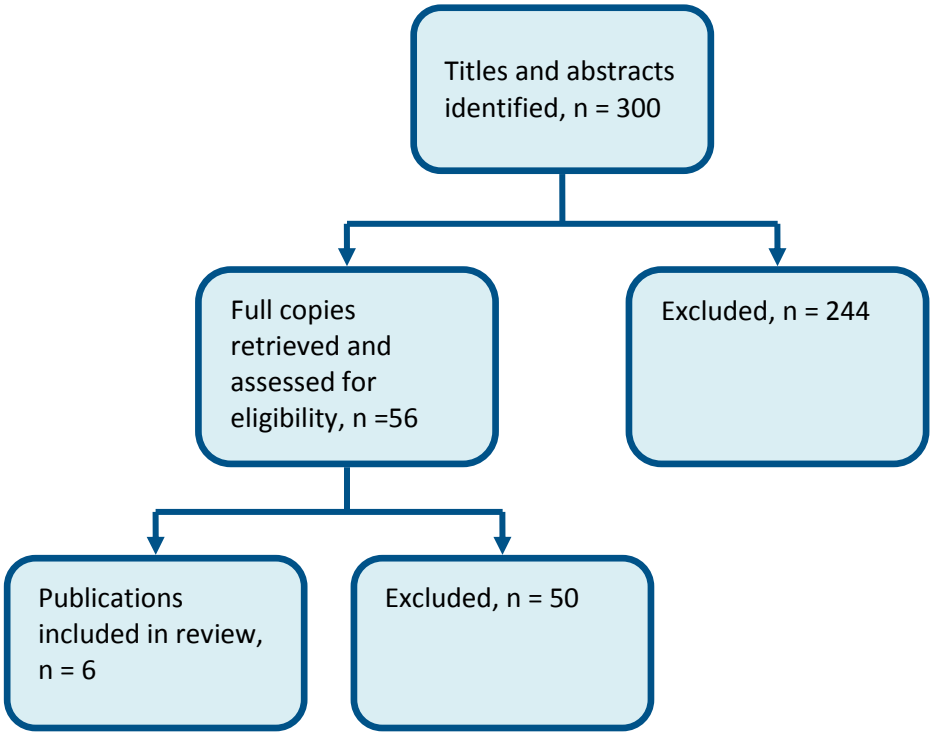
Q.6 Pharmacological interventions

Figure 131: Flow diagram of clinical article selection for pharmacological interventions review



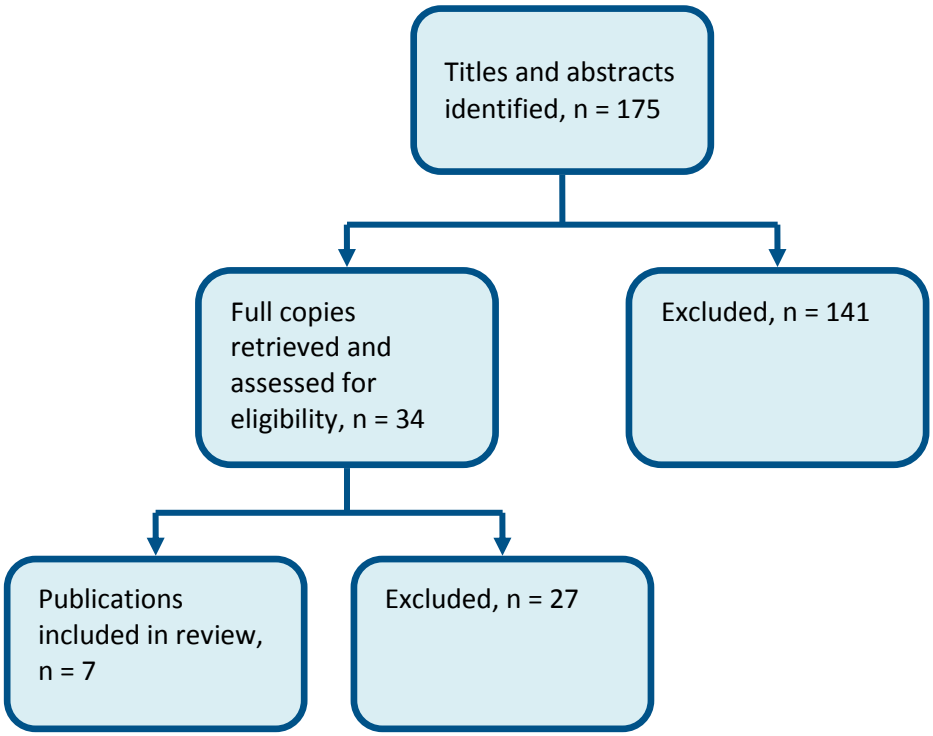
Q.7 Lung transplantation

Figure 132: Flow diagram of clinical article selection for timing of referral for lung transplantation review



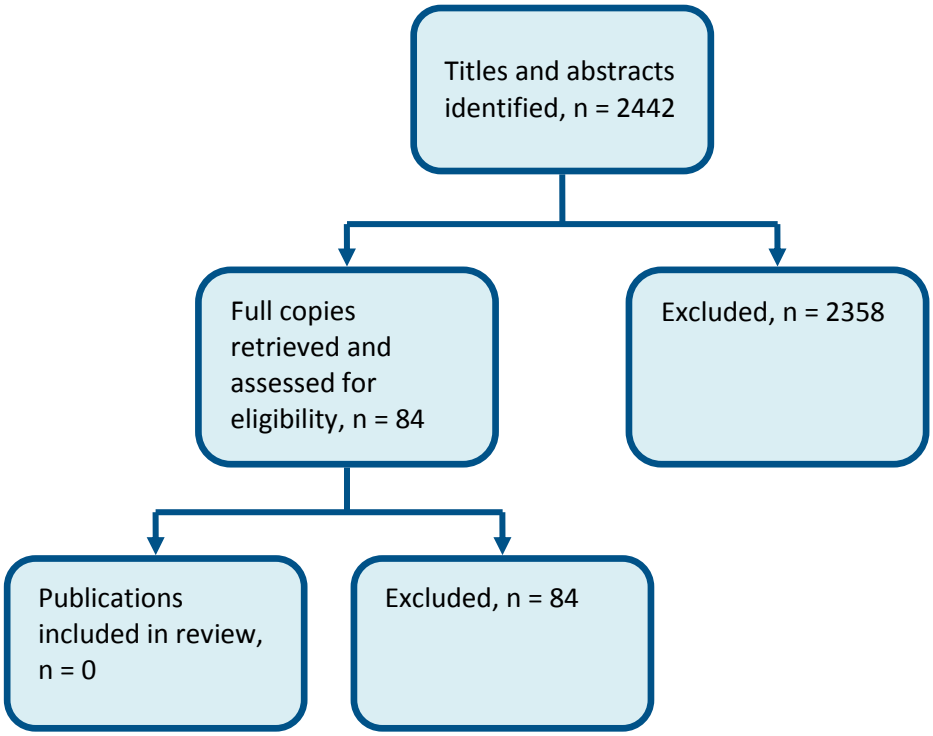
Q.8 Ventilation

Figure 133: Flow diagram of clinical article selection for ventilation review



Q.9 Review and follow-up

Figure 134: Flow diagram of clinical article selection for review and follow-up



Appendix R: Excluded Studies

R.1 Diagnosis

Table 150: Excluded studies for the clinical evidence

Study excluded	Reason
Agostini 2001[9]	No relevant outcomes
Alzeer 2008[17]	Population does not match protocol (ILD of unknown aetiology)
Ayed 2000[25]	No relevant outcomes
Ayed 2003[24]	No relevant outcomes
Behr 2012[36]	Incorrect study design (non-systematic review)
Berbescu 2006[37]	Population does not match protocol (IPF not specified)
Cherniack 1991[64]	Study does not match protocol (pre 1994 data)
Chuang 1987[66]	Study does not match protocol (pre 1994 data)
Cobanoglu 2012[71]	Non English language publication (Turkish)
Collins 1994[79]	Study does not match protocol (pre 1994 data)
Cottin 2012[88]	Incorrect study design (non-systematic review)
Doyle 2012[114]	Incorrect study design (non-systematic review)
Du Bois 2012[123]	Incorrect study design (non-systematic review)
Duck 2007[124]	Incorrect study design (discussion paper)
Esme 2007[132]	No relevant outcomes
Fell 2010[136]	No relevant outcomes
Fend 1989[138]	Study does not match protocol (pre 1994 data)
Fibla 2012[143]	Intervention does not match protocol
Fishbein 2005[145]	Incorrect study design (discussion paper)
Flaherty 2001A[151]	No relevant outcomes
Frankel 2009[155]	Incorrect study design (discussion paper)
Gal 2005[159]	Incorrect study design (discussion paper)
Glaspole 2001A[164]	Incorrect study design (discussion paper)
Gotway 2007[168]	Incorrect study design (discussion paper)
Gruden 1998[169]	Incorrect study design (discussion paper)
Guerra 2009[170]	Non-English language publication (Portuguese)
Hara 2012[175]	Intervention does not match protocol (measurement of S100A9 levels in serum and bronchoalveolar lavage fluid)
Huang 2008[195]	Incorrect study design (discussion paper)
Kataoka 2010[230]	Abstract only (not a full paper)
Kazerooni 1997[232]	Intervention and comparison do not match protocol (incorrect reference standard, CT versus CT)
Keller 1995[234]	Incorrect study design (discussion paper)
Kim 2008[236]	Population does not match protocol (mixed population, ILD and pulmonary nodules)
King 2001A[244]	Study does not match protocol (pre 1994 data)
King 2001A[244]	Study does not match protocol (pre 1994 data)
Kondoh 2006[249]	Population does not match protocol (acute exacerbation)
Kramer 1998[254]	Study does not match protocol (pre 1994 data)

Study excluded	Reason
Kreider 2007[255]	No relevant outcomes
Kulshres 2012[258]	No relevant outcomes
Lee 2009[274]	Abstract only (not a full paper)
Lee 2010[273]	Population does not match protocol (cryptogenic organizing pneumonia)
Lee 2012[271]	Intervention does not match protocol (assessing the levels of pepsin in BAL fluid in IPF patients with acute exacerbation compared to stable disease)
Leslie 2006[275]	Incorrect study design (discussion paper)
Leslie 2012[276]	Incorrect study design (non systematic review)
Lynch 2000[291]	Incorrect study design (discussion paper)
Magpantay 2010[294]	Population does not match protocol (pulmonary tuberculosis)
Mahajan 2002[295]	Incorrect study design (discussion paper)
Maher 2008A[296]	Incorrect study design (discussion paper)
Margaritopoulos 2012[303]	Incorrect study design (non systematic review)
Matsuo 1996[308]	Study does not match protocol (pre 1994 data)
Mazuranic 1996[309]	No relevant outcomes
Melo 2009[312]	Non English language publication (Portuguese)
Meyer 2004[315]	Incorrect study design (discussion paper)
Meyer 2012[316]	Intervention does not match protocol (clinical practice guideline outlining technique for BAL)
Miller 2000[319]	Intervention and comparison do not match protocol (comparison of two biopsy techniques)
Milman 1994[320]	Study does not match protocol (pre 1994 data)
Milman 1995[322]	Population does not match protocol (diffuse pulmonary lesions)
Misumi 2006[323]	Incorrect study design (discussion paper)
Mouroux 1997[332]	Study does not match protocol (pre 1994 data)
Nicholson 2002[353]	Incorrect study design (discussion paper)
Noth 2007[360]	Incorrect study design (discussion paper)
Orens 1995[369]	Intervention does not match protocol (Incorrect reference standard, HRCT)
Park 2007A[378]	No relevant outcomes
Poletti 2004[382]	Incorrect study design (Discussion paper)
Polychronopoulos 2009[385]	Abstract only (not a full paper)
Popp 1992[386]	Study does not match protocol (pre 1994 data)
Popper 2001[387]	Incorrect study design (discussion paper)
Quadrelli 2010[390]	No relevant outcomes
Quigley 2006[391]	Incorrect study design (discussion paper)
Qureshi 2002[394]	No relevant outcomes
Qureshira 2003[393]	No relevant outcomes
Raghu 2004A[399]	Incorrect study design (discussion paper)
Raghu 2004B[396]	Incorrect study design (discussion paper)
Ryu 2007A[417]	Incorrect study design (discussion paper)
Sawy 2004[422]	Population does not match protocol (all patients undergoing a bronchoscopy)
Schmidt 2009A[425]	Incorrect study design (discussion paper)

Study excluded	Reason
Shah 1992[433]	Study does not match protocol (pre 1994 data)
Shah 2008[432]	Incorrect study design (discussion paper)
Shim 2010[436]	No relevant outcomes
Sung 2007[457]	Incorrect study design (discussion paper)
Sverzellati 2009[458]	Abstract only (not a full paper)
Tiitto 2005[471]	No relevant outcomes
Trisolini 2000[478]	Incorrect study design (discussion paper)
Turner 1980[481]	Study does not match protocol (pre 1994 data)
Valeyre 2011[484]	Incorrect study design (discussion paper)
Veeraraghavan 2003[488]	Population does not match protocol and no relevant outcomes (BAL findings used to discriminate between patients with UIP and NSIP)
Wall 1981[492]	Study does not match protocol (pre 1994 data)
Watters 1986[495]	Study does not match protocol (pre 1994 data)
Welker 2004[497]	Intervention does not match protocol (incorrect reference standard, using categorisations for cell differentials)
Zhang 2010[508]	Population does not match protocol (IPF not specified)

Table 151: Excluded studies for the economic evidence

First author	Title	Notes
Molin 1994[328]	VATS increases costs in patients undergoing lung biopsy for interstitial lung disease. Annals of Thoracic Surgery 58 (6):1595-1598, 1994. Thoracic Surgery 58 (6):1595-1598, 1994.	Retrospective study with cost component. Partial applicability - USA retrospective study with cost component. Relevant interventions and population of ILD patients. And very serious limitations- Cost analysis focused on procedural costs only and did not account for relevant costs associated with adverse events of the procedure or subsequent hospital stay. The source of the cost data was not presented. Quality of life not assessed and incremental analysis not presented.

R.2 Prognosis

Table 152: Excluded studies for the clinical evidence

Reference	Reason for exclusion
Alhamad 2008[14]	Analysis does not match protocol (univariable analysis only)
Arcasoy 2003[22]	No relevant outcomes
Augusti 1994[10]	No relevant outcomes
Battista 2003[31]	Non English language publication (Italian)
Best 2003[39]	No relevant outcomes
Boutou 2011[44]	No relevant outcomes
Campainha[55]	Abstract only (not a full paper)
Carbone 2010[56]	Analysis does not match protocol (univariable analysis only)
Chan 1997[60]	Population does not match protocol (cryptogenic fibrosing alveolitis)
Collard 2003[77]	No relevant outcomes
Corte 2009B[84]	Population does not match protocol (diffuse lung disease, not subdivided into IPF)

Reference	Reason for exclusion
Corte 2010A[83]	Population does not match protocol (only 16/90 had IPF; analyses not presented for IPF separately)
Corte 2012[85]	Population does not match protocol (includes IIP considered as IPF, NSIP and interdeterminate IIP; analyses not presented for IPF separately)
Dancer 2012[96]	Incorrect study design (non systematic review)
Devaraj 2009 [109]	Abstract (not a full paper)
Doherty 1997[111]	Population does not match protocol (cryptogenic fibrosing alveolitis)
DuBois 2011 [122]	Analysis does not match protocol (univariable analysis only)
Du Bois 2012[123]	Incorrect study design (non systematic review)
Edey 2011[128]	Population does not match protocol (fibrotic IIP; analyses not presented for IPF separately)
Erbes 1997[131]	Study does not match protocol (pre 1994)
Fakharian 2010 [133]	Abstract only (not a full paper)
Fasano 1999 [134]	Non English language publication (Italian)
Fell 2010[136]	No relevant outcomes
Fernandezperez 2010 [139]	No relevant outcomes
Flaherty 2002[150]	Analysis does not match protocol (univariable analysis only)
Flaherty 2003[147]	Population does not match protocol (fibrotic IIP -UIP and NSIP not distinguished)
Flaherty 2003A[149]	No relevant outcomes
Flaherty 2006[153]	No relevant outcomes
Fujimoto 2012 [156]	Population does not match protocol (all IPF patients with acute exacerbation)
Gay 1998 [161]	Analysis does not match protocol (univariable analysis only)
Harari 1997 [176]	Study does not match protocol (pre 1994)
Holland 2008A[185]	Intervention does not match protocol (RCT looking at the effects of exercise training)
Holland 2010[184]	Abstract (not a full paper)
Hubbard 1998[196]	Population does not match protocol (cryptogenic fibrosing alveolitis)
Huie 2011 [197]	Abstract only (not a full paper)
Hwang 2011[199]	Population does not match protocol (IPF not specified)
Ichikado 2002 [200]	Population does not match protocol (acute interstitial pneumonia)
Iwasawa 2008 [205]	Non English language publication (Japanese)
Iwasawa 2009 [206]	Intervention does not match protocol (used the Gaussian histogram normalised correlation system to determine the extent of disease on CT images)
Jastrzebski 2005A[215]	Population and prognostic factor does not match protocol (all lung transplant referrals and left ventricular ejection fraction)
Jegal 2005[218]	Population does not match protocol (fibrotic IIP, UIP and NSIP not distinguished)
Jeong 2005 [220]	Analysis does not match protocol (univariable analysis only)
Kaminsky 2007[228]	No extractable data (No OR, RR or HR)
Kim 2010B[237]	Abstract only (not a full paper)
King 2001[243]	No relevant outcomes
Kishaba 2012[245]	No relevant outcomes
Kurashima 2010 [260]	Abstract only (not a full paper)
Kawut 2005[231]	Population does not match protocol (indirect population, 55% UIP only)
Lama 2003[262]	No relevant outcomes

Reference	Reason for exclusion
Laz 2011 [269]	Abstract only (not a full paper)
Lederer 2006[270]	No relevant outcomes
Lettieri 2006 [277]	Intervention does not match protocol (right heart catherterisation to measure PAH)
Lettieri 2006A[278]	No relevant outcomes
Ley 2012[282]	Intervention does not match protocol (development and validation of a staging system, data not presented for FVC in patient's with IPF alone)
Manali 2010[299]	No relevant outcomes
Miller 2012[318]	Incorrect study design (non-systematic review)
Moloney 2003[331]	Intervention does not match protocol (reliability of the SWT measuring functional capacity in patients with IPF)
Nadrous 2005 [335]	No relevant outcomes
Nadrous2005A [334]	No relevant outcomes
Nagao 2002 [337]	Study does not match protocol (pre 1994)
Nathan 2007[341]	No relevant outcomes
Nathan 2008A [343]	No relevant outcomes
Nathan 2011A [342]	No relevant outcomes
Latsi 2003[267]	No relevant outcomes and population does not match protocol (UIP versus NSIP)
Peelen 2010[380]	Population does not match protocol (fibrotic IIP, UIP and NSIP not distinguished)
Riha 2002[411]	No relevant outcomes and population does not match protocol (UIP versus NSIP)
Ryerson 2011[414]	No relevant outcomes
Screaton 2005 [430]	Population does not match protocol (not IPF)
Shabbier 2012	Intervention does not match protocol (sensitivity and specificty of HRCT scans, not the prognostic implications of HRCT features and patterns)
Shin 2008 [437]	Population does not match protocol (not IPF)
Sumikawa 2006 [455]	No relevant outcomes
Schwartz1994A[428] Schwartz1994B[429]	No relevant outcomes
Swigris 2010A[463]	No relevant outcomes
Swigris 2009 [462]	No relevant outcomes
Valeyre 2010[485]	Intervention does not match protocol (responsiveness to pharmacological treatment)
Xaubet 1998 [500]	No relevant outcomes
Yang 2009 [502]	Non English language publication (Chinese)
Zisman 2007 [513]	No relevant outcomes
Zisman 2007A [514]	Intervention does not match protocol (prediction of pulmonary hypertension)
Zompatori 2003[515]	No relevant outcomes

Excluded studies for the economic evidence:

No health economic literature assessing an intervention for a prognostic purpose in an IPF population was identified. No studies were selectively excluded.

R.3 Pulmonary rehabilitation

Table 153: Excluded studies for the clinical evidence

Reference	Reason for exclusion
Bausewein2008C[34]	Intervention and population do not match protocol (Cochrane review, no studies included had IPF/ILD people or used PR as an intervention)
Bevelaqua2011[40]	Population do not match protocol (ILD not specified)
Budweiser2006 [50]	Population does not match protocol (restrictive lung disease doesn't analysis results for ILD/IPF separately)
Butcher2001[51]	Population does not match protocol (primarily COPD, 9/49 pulmonary fibrosis and were not analysed separately)
Cockcroft1981[73]	Population does not match protocol (coal workers with pneumoconiosis and chronic obstructive airway disease)
Cockcroft1982[72]	Population does not match protocol (people had coal workers pneumoconiosis and COPD)
Connor 2007[81]	Population does not match protocol (restrictive lung disease which includes ILD and thoracic skeletal abnormalities, ILD not analysed separately)
Dierich2010[110]	Population and outcomes do not match protocol (mixed ILD population and analyses of VC and 6MWT is not presented for IPF separately)
Ferreira 2000[142]	Population does not match protocol (COPD vs. non COPD, does not analyse results for IPF/ILD separately)
Fowler2011[154]	Population and outcomes do not match protocol (ILD proportion of included population not specified and results for shuttle walk test not presented)
Ho2010[182]	Population does not match protocol (ILD not specified)
Holden 1990[183]	Population does not match protocol (not IPF)
Jastrzebski2007A[216]	Intervention does not match protocol (inspiratory muscle training versus no inspiratory muscle training in isolation)
Jastrzebski2008[217]	Non-English language publication (Polish)
Kagaya 2009[227]	Population does not match protocol (cannot determine proportion of people with IPF/ILD)
Kozu 2011B[252]	Intervention does not match protocol (effectiveness of PR programmes according to the severity of dyspnoea)
Lindell 2010[285]	Intervention does not match protocol (psychosocial support no PR is included; this paper has been included in the psychosocial support section of the guideline).
Marciniak2010[302]	Intervention and population does not match protocol (weight management programme for people with obesity people and no further information provided on population)
Mittal 2011[324]	Population does not match protocol (did not analyse results for people with IPF/ILD people separately)
Ochmann2012[364]	Incorrect study design (non systematic review)
Rozanski2012[413]	Population and outcomes do not match protocol (mixed ILD population post lung tranplantation and analyses of 6MWT is not presented for IPF separately)
Salhi 2010[420]	Population does not match protocol (restrictive lung disease, 6/31 people had pulmonary fibrosis and results have not been analysed separately for IPF/ILD)

Reference	Reason for exclusion
Verrill2008[490]	Population does not match protocol (does not specify if people with IPF/ILD are included)
Verrill2008A[491]	Intervention does not match protocol (validating a prediction equation)
Warrington 2010[494]	Intervention does not match protocol (PR with and without oxygen)

Excluded studies for the economic evidence:

No relevant economic evaluations that assessed pulmonary rehabilitation in an IPF population were identified. No studies were selectively excluded.

R.4 Best supportive care

Table 154: Excluded studies for the clinical evidence

Reference	Reason for exclusion
Agarwal 2009[8]	Not relevant to clinical question (review of ILD and sleep)
Alhamad 2009[13]	Population does not match protocol (sarcoidosis)
Allen 2005[15]	Incorrect study design (not an intervention study)
Annane 2007[18]	Population and intervention do not match protocol and intervention (no IPF/ILD and intervention is mechanical ventilation)
Aversa 1993[23]	Population does not match protocol (only 6/73 pulmonary fibrosis; majority COPD)
Bailey 2010[27]	Incorrect study design (not an intervention study)
Bajwah 2012[29]	Incorrect study design (not an intervention study)
Barlo 2009[30]	Non English language publication (Dutch)
Baughman 2005[32]	Population does not match protocol (sarcoidosis)
Baughman 2006A[33]	Population and intervention does not match protocol (infliximab therapy in sarcoidosis)
Bevelaqua 2011[40]	Population does not match protocol (end stage lung disease, ILD/IPF not specified)
Braghiroli 1993[45]	No relevant outcomes. (This study contains the protocol of a study which is included in Crockett 2001[22] & Zielinski 2000[83])
Brown 2006[49]	Incorrect study design (not an intervention study)
Cerri 2012[58]	Incorrect study design (not an intervention study)
Chailleux 1996[59]	Does not match review question (not relevant to patient review or best supportive care)
Chang 1999[61]	Does not match review question (description of HRQoL)
Choi 2008[65]	Incorrect study design (dissertation)
Cima 2010[67]	Population does not match protocol (not IPF)
Clark 2001[69]	Does not match review question (descriptive study of prevalence of cough in IPF)
Coelho 2010[74]	Does not match review question (QOL in IPF and no intervention)
Corte 2009[82]	Does not match review question (mortality prediction by nocturnal desaturation)
Crockett 1991[91]	Population does not match protocol (majority COPD)
Currow 2008[94]	Population does not match protocol and does not match review question (majority COPD)
Dayton 1993[99]	Does not match review question and study does not match protocol (pre-1994)

Reference	Reason for exclusion
Dayton 1993[99]	Does not match review question (not relevant to patient review or best supportive care)
Douglas 2000[113]	Incorrect study design and does not match review question (observational study looking at prognostic factors)
Dubois 1999[120]	Population does not match protocol (sarcoidosis)
Duck 2008[125]	Incorrect study design (non-systematics review)
Duck 2009[126]	Incorrect study design (non-systematics review)
Eaton 2001[127]	Population does not match protocol (majority COPD)
Fasciolo 1994[135]	Population does not match protocol (only 17/104 pulmonary fibrosis; majority COPD/ cancer)
Fakharian 2010[133]	Does not match review question (not best supportive care)
Harris-Eze 1994[177]	No relevant outcomes
Harris-Eze 1995[178]	No relevant outcomes
Hira 1997[180]	Incorrect study design (not an intervention study)
Hirst 2001[181]	Does not match review question (insomnia)
Ho 2010[182]	Population does not match protocol (restrictive lung disease, ILD/IPF not specified)
Hook 2012[190]	Does not match review question (not relevant to patient review or best supportive care)
Irwin 1998[203]	Does not match review question (management of cough; not specific to IPF)
Janssen 2010[211]	Incorrect study design and population does not match protocol (case series and majority COPD)
Janssens 1996[212]	Comparison does not match protocol (comparative evaluation with COPD patients)
Jastrzebski 2005[214]	Does not match review question (QOL in patientss awaiting lung transplantation)
Johnson 1989[222]	Does not match review question and study does not match protocol (pharmacological study, pre-1994)
Judson 2006[224]	Population does not match protocol (sarcoidosis)
Kagan 1976[226]	Population does not match protocol (not IPF/ILD)
Kastelik 2005[229]	Does not match review question (chronic cough; not specific to IPF)
Krishnan 2008[256]	Does not match review question (sleep quality and HRQoL description only)
Kumar 2010[259]	Incorrect study design and population does not match protocol (not an intervention study and not IPF)
Kyeong 1999[261]	Non English language publication (Korean)
Lamas 2011[264]	Does not match review question (delay in initial assessment)
Lancaster 2009[265]	Incorrect study design (descriptive study only, no intervention)
Lindell 2007[283]	Incorrect study design (no intervention)
Louly 2009[287]	Incorrect study design (case study)
Lower 2008[288]	Population does not match protocol (sarcoidosis)
Mahler 1989[298]	Population does not match protocol (ILD population only)
Martinez 2000[305]	Does not match review question (evaluation of SF36 in IPF)
Martinez 2005[304]	Does not match review question (clinical course of IPF)
Masjedi 2010[306]	Incorrect study design (no intervention)
Mermigkis 2009[314]	Incorrect study design (observational study, no intervention)
Milman 1994A[321]	Population does not match protocol (sarcoidosis)
Papiris 2005[377]	Incorrect study design (descriptive study only, no intervention)
Polosa 2002[384]	Does not match review question (X

Reference	Reason for exclusion
Polonski 1994[383]	No relevant outcomes
Rank 2007[406]	Incorrect study design (no intervention)
Ryerson 2011[414]	Does not match review question (prognostic study of cough)
Ryerson 2012[416]	Incorrect study design (no intervention)
Ryerson 2012A[415]	Systematic review- all relevant papers have been included in the guideline
Saydain 2002[423]	Incorrect study design (descriptive study only, no intervention)
Sharifabad 2010[435]	Population does not match protocol (chronic lung disease, IPF not specified)
Shulgina 2011[440]	Does not match review question (not relevant to patient review or best supportive care)
Simon2012[443]	Population does not match protocol (not IPF)
Sundar 2010[456]	Does not match review question (prevalence of cough in conditions other than IPF)
Swigris 2005A[466]	Does not match review question (background to IPF QoL tools)
Swigris 2005B[461]	Does not match review question (not relevant to patient review or best supportive care)
Swigris 2011[465]	Does not match review question (not relevant to patient review or best supportive care)
Troy 2012[479]	Does not match review question (sleep disordered breathing in IPF)
Wee 2011[496]	Population does not match protocol (no ILD /IPF populations included in any of the studies included in this review)
Xaubet 2001[499]	Does not match review question (delay in initial assessment)

Table 155: Excluded studies for the economic evidence

Reference	Reason for exclusion
M. Neri, L. Fedi, A. Spanevello, G. Mazzucchelli, M. Grandi, M. Ambrosetti, S. Conti, and G. B. Migliori. Savings obtained using an oxygen economizer device: a cost-minimization analysis. Monaldi Archives for Chest Disease 54 (4):311-314, 1999.	This cost minimisation analysis evaluates the use of oxygen minimiser device in the administration of liquid oxygen. This study was selectively excluded on not assessing a relevant population (Only 4 of 29 patients in the sample had restrictive lung disease).

R.5 Psychosocial support

Table 156: Studies excluded from the clinical review

Reference	Reason for exclusion
Anon 2005[2]	Does not match review question (patient information on a clinical trial)
Bajwah 2011[28]	Poster presentation only (not a full paper)
Blake 1990[41]	Population does not match protocol (chronic lung disease, IPF not specified)
Carroll 1999[57]	Incorrect study design (no intervention)
Coffman 2002[75]	Does not match review question (review of psychiatric issues and pulmonary disease, no intervention)
Cox 2004[90]	Population does not match protocol (no ILD/ IPF patients)
Daniels 2006[97]	Intervention does not match protocol (review of management of patients with IPF)
Drent 1998[115]	Population does not match protocol (sarcoidosis)

Reference	Reason for exclusion
Dressel 2007[116]	Population does not match protocol (no ILD/ IPF patients)
Duck 2008[125]	Intervention does not match protocol (review of management of patients with IPF)
Duck 2009[126]	Intervention does not match protocol (review of management of patients with IPF)
Egan 2011[129]	Intervention does not match protocol (review of management of patients with IPF)
Holden 1990[183]	Population does not match protocol (no ILD/ IPF patients)
Jain 2009[209]	Does not match review question (review of psychiatric issues and pulmonary disease, no intervention)
Killin 2010[235]	Poster presentation only (not a full paper)
Krishnan 2008[256]	Does not match review question (sleep quality and HRQoL description only, no intervention)
Lee 2011[272]	Intervention does not match protocol (review of management of patients with IPF)
Lindell 2007[283]	Study included in Lindell 2010[285]
Michaelson 2000[317]	Intervention does not match protocol (review of management of patients with IPF)
Ong 2001[367]	Population does not match protocol (majority COPD)
Prendergast 2002[388]	Incorrect study design (no intervention, case studies)
Pruitt 2008[389]	Does not match review question (overview of restrictive lung diseases)
Quill 2000[392]	Incorrect study design (no intervention, case studies)
Ryerson 2011[414]	Does not match review question (study looking at the association between dyspnea and depression)
Shanmugam 2007[434]	Does not match review question (overview of psychiatric consideration in pulmonary diseases)
Shipley 2009[438]	Does not match review question (study to examine the use of a screening test to identify depression in an ILD population)
Swigris 2005[467]	Does not match review question (validation study of SF-36 for measuring HRQoL)
Swigris 2005A[466]	Does not match review question (background to IPF QoL tools)
Swigris 2005B[461]	Does not match review question (not relevant to psychosocial support)
Tomioka 2007[475]	Does not match review question (study developing a HRQoL instrument)
Verrill 2008[490]	Population does not match protocol (majority COPD)
Yeager 2005[503]	Population does not match protocol (sarcoidosis)

R.6 Pharmacological interventions

Table 157: Excluded studies for the clinical evidence

Reference	Reason for exclusion
Actelion 2004[7]	Abstract only (original paper has been considered King 2008A[239])
Antoniu 2008A[19]	Abstract only (original paper has been considered King 2008A[239])
Behr 2002[35]	Incorrect study design and no relevant outcomes (study not randomised)
Brown 2008[48]	Commentary on King 2008A[239]
Collard 2007[76]	Incorrect study design (not RCT)
Costabel 2011[86]	Non-English language publication (German)
Du Bois 2006[119]	Abstract for King 2008A[239]
Flaherty 2004 [148]	Intervention does not match protocol (zileuton)
Han 2011[174]	Population does not match protocol (pulmonary hypertension)

Reference	Reason for exclusion
Homma 2010[188]	Abstract of study already in file [189]
Jackson 2009[208]	Abstract of study already in file (Jackson 2010[207])
King 2006[240]	Abstract for King 2008A[239]
King 2008[238]	Incorrect study design (discussion paper)
King 2010[241]	Abstract for King 2011[242]
Lavender 2011[268]	Editorial of trial already included in guideline
Meiersydow 1979[310]	Non-English language publication (German)
Miyazaki1y 2011[325]	Intervention does not match protocol (cyclosporine A versus cyclophosphamide with corticosteroid)
Nagai 2008[336]	Incorrect study design (non-systematic review)
Nathan 2006[340]	Incorrect study design (non-systematic review)
Newman 2011A[350]	Does not match review question (assessment of whether thiopurine methyltransferase genotyping prior to azathioprine reduces adverse drug reactions)
Nicholson 2007[354]	Subset of King 2008[238]
O'Connell 2011[362]	Incorrect study design (non-systematic review)
Papali 2010 [376]	Incorrect study design (non-RCT)
Raghu 2006[397]	Abstract for King 2008A[239]
Raghu 2008[398]	Intervention does not match protocol (etanercept)
Raghu 2010[401]	Subset of King 2008[238]
Richeldi 2012[409]	Incorrect study design (non-systematic review)
Roig2010[412]	Non-English language publication (Spanish)
Ryerson 2012[416]	Incorrect study design (not RCT)
Scriabine 2009[431]	Incorrect study design (Not RCT)
Stolagiewicz 2012[450]	Incorrect study design (Cochrane protocol)
Swigris 2008[460]	Incorrect study design (Not RCT)
Tomioka 2003[474]	Abstract of Tomioka 2005[476]
Tzouvelekis 2011[483]	Incorrect study design (retrospective cohort)
Varney 2008[487]	Population does not match protocol (IPF patients not analysed separately)
Velluti 2000[489]	No relevant outcomes
Walter 2006[493]	Incorrect study design (non-systematic review)
Zisman 2010A[511]	Abstract of study already in file [512]

Excluded studies for the economic evidence:

No studies were selectively excluded.

R.7 Lung transplantation

Table 158: Excluded studies for the clinical evidence

Reference	Reason for exclusion
Caminati 2010[54]	Incorrect study design and does not match review question (non-systematic review on the diagnosis and prognosis of IPF)
Costache 2009[87]	Intervention does not match protocol and the population does not match

Reference	Reason for exclusion
	protocol (study does not look at referral times/severity level of disease and results for IPF not separated)
Daniels 2006[97]	Incorrect study design (non-systematic review)
Davis 1994[98]	Intervention does not match protocol (investigates the results after lung transplantation)
Demeester 2001[100]	Intervention does not match protocol and population does not match protocol (life expectancy and lung transplant effect and results for IPF not separated)
Deoliveira 2012a[102]	Intervention does not match protocol (effectiveness of type of lung transplant, single versus bilateral)
Deoliveira 2012b[101]	Intervention and population do not match the protocol (ILD population with no stratification for IPF, outcomes of patients who underwent single lung and bilateral LTX)
Egan 1991[130]	Intervention does not match protocol (analyses referrals to a single centre for lung transplantation)
Feltrim 2008[137]	Intervention does not match protocol (QoL of patients on lung transplantation waiting list)
Fioret 2011[144]	Incorrect study design (non-systematic review on the management of IPF)
Genao 2012[162]	Intervention does not match protocol (trajectory of function after lung transplantation in old and young recipients in the post lung allocation score era and abstract only)
George 2011[163]	Intervention does not match protocol (no information on stage or timing of referral)
Gottlieb 2012[167]	Intervention does not match protocol (outcomes of ventilated transplant patients and the results aren't separated out for IPF patients)
Gomez 2003[165]	Population does not match protocol (does not specify IPF)
Hayden 1993[179]	Population does not match protocol (does not analyse IPF patients separately)
Jastrzebski 2005[214]	Intervention does not match protocol (QoL of patients on a lung transplantation waiting list)
Jastrzebski 2005a[215]	Population does not match protocol (does not analyse IPF patients separately)
Keating 2009[233]	Intervention does not match protocol (no mention of timing of referral)
King 2001[243]	Intervention does not match protocol (prognostic study looking at survival in IPF patients)
Klooster 2011[246]	Abstract only (not a full paper)
Kozower 2008[251]	Intervention does not match protocol (survival of IPF patients is not captured pre and post LAS implementation)
Lalaatsp 1998[1]	Guideline: all relevant papers have already been included/considered
Lamas 2011[264]	Intervention does not match protocol (referral time to sub-speciality care not specifically LTX referral)
Lamas 2011a[263]	Abstract only (full paper assessed LAMAS 2011[264])
Langer 2012[266]	Intervention does not match protocol (investigates the level of activity in patients who are candidates for lung transplantation)
Lederer 2006[270]	Intervention does not match protocol (does not look at referral times/severity level of disease)
Levvey 2009[281]	Abstract only (not a full paper)
Ley 2011[264]	Intervention does not match protocol (development of a staging system)
Lingaraju 2006[286]	Intervention does not match protocol (survival of IPF patients is not captured pre and post LAS implementation)

Reference	Reason for exclusion
Lutogniewska 2010[290]	Intervention does not match protocol (QoL and dyspnoea in patients referred for lung transplantation)
Mackay 2007[293]	Population does not match protocol (does not analyse IPF patients separately)
Mahida 2012[297]	Incorrect study design (non-systematic review)
Mansour 2011[301]	Abstract only and intervention does not match protocol (difference in outcomes for lung transplantation in patients with IPF who had an acute exacerbation)
Martinez 2005[304]	Intervention does not match protocol (clinical course of IPF patients, no mention of referral times)
Mason 2007[307]	Intervention does not match protocol does (compares survival of IPF patients versus non IPF receiving lung transplantation)
Merlo 2009[313]	Intervention does not match protocol (of IPF patients is not captured pre and post LAS implementation)
Nathan 2005b[339]	Incorrect study design (non-systematic review)
Obeirne 2010[361]	Incorrect study design (non-systematic review)
Orens 2006[370]	Guideline: all relevant papers have already been included/considered
Osaki 2009[372]	Abstract only and population does not match protocol (does not analyse IPF patients)
Osaki 2010[371]	Population does not match protocol (does not analyse IPF patients separately)
Reed 2006[407]	Intervention does not match protocol (does not analyse IPF patients separately)
Santana 2009[421]	Intervention does not match protocol (improvements in QOL after transplantation)
Shitrit 2009[439]	Intervention does not match protocol (study on the 15-step oximetry test)
Stavem 2000[448]	Intervention does not match protocol (QoL of patients on lung transplantation waiting list and recipients)
Studer 2000[451]	Incorrect study design (non-systematic review)
Thabut 2003[469]	Intervention does not match protocol (survival benefits of lung transplantation)
Titman 2009[472]	P population does not match protocol (diffuse parenchymal lung disease, doesn't specify IPF)
Tuppin 2008[480]	Population does not match protocol (does not analyse IPF patients separately)
Whelan 2005[498]	Does not match review question (prognostic value of pulmonary artery pressure)

Table 159: Excluded studies for the economic evidence

Reference	Reason for exclusion
S. D. Ramsey, D. L. Patrick, R. K. Albert, E. B. Larson, D. E. Wood, and G. Raghu. The cost-effectiveness of lung transplantation: a pilot study. Anonymous. Anonymous. Chest 108(6):1594-1601, 1995.	Within trial CUA from USA Medicare perspective based on case findings. Excluded due to a low proportion of the sample having IPF (n=5/26)

R.8 Ventilation

Table 160: Excluded studies for the clinical evidence

Reference	Reason for exclusion
Altinoz 2010[16]	Non-English language publication (Turkish)

Reference	Reason for exclusion
Blancal 2010[42]	Abstract only and intervention does not match the protocol (studies the clinical feature and prognostic factors of acute exacerbation of IPF)
Claudett 2010[70]	Intervention does not match protocol (protocol used for NIMV)
Fernandez 2008[140]	Intervention does not match protocol (setting for MV)
Fumeaux 2003[158]	Non-English language publication (French)
Gottlieb 2010[166]	Abstract only (the original paper Gottlieb 2012[11] has been considered)
Gottlieb 2012[167]	Population and intervcention does not match protocol (analysis of prognostic markers of ventilated patients who are lung transplantation candidates and IPF not separated in the analysis)
Howard 2009[194]	Abstract only and intervention does not match protocol (overview of NIMV and its effectiveness in a range of conditions)
Iotti 2010[202]	Population and intervention does not match protocol, the study does not specify if IPF patients are present in the sample. And the Intervention does not match protocol the study compares two different types of MV
Jin 2008[221]	Non-English language publication (Korean).
Koschel 2010[250]	Population and intervention does not match protocol (IPF not separated and study looks at the acute effects of NIMV)
Lunt 2011[289]	Abstract only and population does not match protocol (ILD, n=1)
Moderno 2010[326]	Intervention does not match protocol (effects of NIMV on exercise performance)
Mollica 2008[329]	Incorrect study design (non-systematic review)
Niwa 2010[356]	Abstract only and population does not match protocol (acute respiratory distress syndrome)
Niwa 2011[357]	Intervention does not match protocol (safety of a new ventilation system in patients with interstitial pneumonia)
Pandey 2011[375]	Population and intervention does not match protocol (ILD, n=1 and benefits of NIMV)
Rai 2004[403]	Population does not match protocol (ILD, n=2)
Rangappa 2009[405]	Intervention does not match protocol (outcomes of IPF patients admitted to ICU)
Ryerson 2012[416]	Systematic review (all relevant papers have already been included/considered)
Sakamoto 2011[419]	Intervention does not match protocol (incidence of acute exacerbation after lung transplantation)
Schönhofer 1997[427]	Intervention does not match protocol (use of MV during the day versus the night)
Su 2010[452]	Non-English language publication (Chinese)
Suh 2006[453]	Population does not match protocol (interstitial pneumonia)
Tomii 2010[473]	Population does not match protocol (interstitial pneumonia)
Yokoyama 2011[505]	Abstract only and intervention and population do not match the protocol (effect of early NIMV in acute exacerbation of interstitial pneumonia)
Yokoyama 2012[506]	Population does not match protocol (interstitial pneumonia)

Excluded studies for the economic evidence:

No relevant economic evaluations comparing invasive and non-invasive ventilation strategies were identified. No studies were selectively excluded.

Patient review and follow-up

Table 161: Excluded studies for the clinical evidence

Reference	Reason for exclusion
Agarwal 2009[8]	Does not match review question (review of ILD and sleep)
Alhamad2009[13]	Population does not match protocol (sarcoidosis)
Allen 2005[15]	Incorrect study design (not an intervention study)
Annane 2007[18]	Incorrect population, no IPF/ILD and intervention is mechanical ventilation
Aversa 1993[23]	Incorrect population, only 6/73 pulmonary fibrosis; majority COPD
Bailey 2010[27]	Incorrect study design (not an intervention study)
Bajwah 2012[29]	Incorrect study design (not an intervention study)
Barlo 2009[30]	Non English lauguage publication (Dutch)
Baughman 2005[32]	Population does not match protocol (sarcoidosis)
Baughman 2006A[33]	Population and intervention does not match protocol (infliximab therapy in sarcoidosis)
Bevelaqua 2011[40]	Does not match review question (not relevant to patient review or best supportive care)
Brown 2006[49]	Incorrect study design (not an intervention study)
Cerri 2012[58]	Incorrect study design (not an intervention study)
Chailleux 1996[59]	Does not match review question (not relevant to patient review or best supportive care)
Chang 1999[61]	Does not match review question (description of HRQoL)
Choi 2008[65]	Incorrect study design (dissertation)
Cima 2010[67]	Incorrect population, not IPF
Clark 2001[69]	Does not match review question (descriptive study of prevalence of cough in IPF)
Coelho 2010[74]	Does not match review question (QoL in IPF)
Corte 2009[82]	Does not match review question (mortality prediction by nocturnal desaturation)
Crockett 1991[91]	Population does not match protocol (majority COPD)
Crockett 2001[92]	Does not match review question (not relevant to patient review or best supportive care)
Currow 2008[94]	Population does not match protocol (majority COPD)
Currow 2011[93]	Does not match review question (not relevant to patient review or best supportive care)
Dayton 1993[99]	Study does not match protocol (pre 1994)
Dayton 1993[99]	Does not match review question (not relevant to patient review or best supportive care)
Douglas 2000[113]	Does not match review question (not relevant to patient review or best supportive care)
Dubois1999[120]	Population does not match protocol (sarcoidosis)
Duck 2008[125]	Incorrect study design (not an intervention study)
Duck 2009[126]	Incorrect study design (not an intervention study)
Eaton 2001[127]	Population does not match protocol (majority COPD)
Fakharian 2010[133]	Abstract only (not a full paper)
Fasciolo1994[135]	Population does not match protocol (majority COPD and cancer)
Harris-Eze 1994[177]	No relevant ouctomes
Harris-Eze 1995[178]	No relevant ouctomes

Reference	Reason for exclusion
Hira 1997[180]	Incorrect study design (not an intervention study)
Hirst 2001[181]	Does not match review question (insomnia)
Ho 2010[182]	Does not match review question (not relevant to patient review or best supportive care)
Hook 2012[190]	Does not match review question (not relevant to patient review or best supportive care)
Hope-Gill 2003[191]	Does not match review question (not relevant to patient review or best supportive care)
Horton 2008[192]	Incorrect study design (letter)
Irwin 1998[203]	Doesnot match review question (management of cough, not specific to IPF)
Janssen 2010[211]	Population does not match protocol (majority COPD)
Janssens 1996[212]	Comparison does not match protocol (comparative evaluation with COPD patients)
Jastrzebski 2005[214]	Does not match review question (QoL in patients awaiting lung transplantation)
Johnson 1989[222]	Study and intervention does not match protocol (pre-1994 and a pharmacological study)
Judson 2006[224]	Population does not match protocol (sarcoidosis)
Kagan 1976[226]	Population does not match protocol (no IPF/ILD)
Kastelik 2005[229]	Intervention does not match protocol (chronic cough not specific to IPF)
Krishnan 2008[256]	Does not match review question (sleep quality and HRQoL description only)
Kumar 2010[259]	Incorrect study design and population does not match protocol (not an intervention study and not IPF
Kyeong 1999[261]	Non English language publication (Korean)
Lamas 2011[264]	Intervention does not match protocol (delay in initial assessment)
Lancaster 2009[265]	Incorrect study design (not an intervention study)
Lindell 2007[283]	Incorrect study design (not an intervention study)
Lindell 2007A[284]	Abstract only (not a full paper)
Louly 2009[287]	Incorrect study design (case study)
Lower 2008[288]	Population does not match protocol (sarcoidosis)
Mahler 1989[298]	Study and population does not match protocol (pre-1994 and ILD only)
Martinez 2000[305]	Intervention does not match protocol (evaluation of SF36 in IPF)
Martinez 2005[304]	Does not match review question (paper outlining clinical course of IPF)
Masjedi 2010[306]	Incorrect study design (not an intervention study)
Mermigkis 2009[314]	Incorrect study design (not an intervention study)
Milman1994A[321]	Population does not match protocol (sarcoidosis)
Papiris 2005[377]	Incorrect study design (not an intervention study)
Polonski 1994[383]	Abstract only (not a full paper)
Polosa 2002[384]	See Cochrane review using Harris-Eze 1995[178]
Rank 2007[406]	Incorrect study design (not an intervention study)
Ryerson 2011[414]	Does not match review question (prognostic study of cough)
Ryerson 2012[416]	Incorrect study design (not an intervention study)
Ryerson 2012A[415]	No extra papers found to include from review
Saini 2011[418]	Abstract only (not a full paper)
Saydain 2003[423]	Incorrect study design (not an intervention study)

Reference	Reason for exclusion
Sharifabad 2010[435]	Population does not match protocol (majority COPD)
Shulgina 2011[440]	Does not match review question (not relevant to patient review or best supportive care)
Simon 2010[443]	Population does not match protocol (not IPF)
Sundar 2010[456]	Does not match review question (prevalence of cough in conditions other than IPF)
Swigris 2005A[466]	Does not match review question (background to IPF QoL tools)
Swigris 2005B[461]	Does not match review question (not relevant to patient review or best supportive care)
Swigris 2011[465]	Does not match review question (not relevant to patient review or best supportive care)
Swinburn 1991[468]	Does not match review question (effect of O2 on ILD)
Troy 2012[479]	Does not match review question (sleep disordered breathing in IPF)
Xaubet 2001[499]	Does not match review question (delay in initial assessment)
Zielinski 2000[509]	See Crockett Cochrane review[89]

Excluded studies for the economic evidence:

No relevant economic evaluations comparing different review and monitoring strategies were identified. No studies were selectively excluded.

Appendix S: Reference list

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