2-year surveillance 2015 – Idiopathic pulmonary fibrosis (2013) NICE guideline CG163

Appendix A: decision matrix

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
Awareness of clinical features of idiopathic pulmonary fibrosis (IPF); Diagnosis; Information and support		
163 – 01 In suspected IPF what is the value of adding biopsy to clinical evaluation, PFTs, CT +/- bronchoalveolar lavage for confirming the diagnosis of IPF? (1.1.1, 1.2.1–1.2.7 1.3.1)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
163 – 02 In suspected IPF what is the value of adding multidisciplinary team (MDT) consensus to clinical assessment, PFTs and CT in the diagnosis of IPF? (1.1.1, 1.2.1–1.2.7 1.3.1)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
163 – 03 How and by whom is a MDT diagnostic consensus best achieved (i.e. constituency of the MDT, specialist clinics, networks) (1.1.1, 1.2.1–1.2.7 1.3.1)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Information and support		
163 – 04 What is the specific type of psychosocial support and information that should be provided for patients diagnosed with IPF? (1.3.2–1.3.4)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
Prognosis		
163 – 05 Do serial pulmonary function tests (PFTs) (resting spirometric, gas transfer measurement and oxygen saturation) predict prognosis of IPF? (1.4.1–1.4.3, 1.3.1)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
163 – 06 Does baseline sub-maximal exercise testing predict prognosis of IPF? (1.4.1–1.4.3, 1.3.1)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
163 – 07 Does baseline echocardiography predict prognosis of IPF? (1.4.1–1.4.3, 1.3.1)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
163 – 08 Do baseline CT scores predict prognosis of IPF? (1.4.1–1.4.3, 1.3.1)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Management – pulmonary rehabilitation		
163 – 09 What are the benefits of pulmonary rehabilitation programmes for people with confirmed IPF? (1.5.1–1.5.4)		
In an RCT[1], people with IPF (n=21) were randomised to pulmonary rehabilitation or to control. Pulmonary rehabilitation consisted of 90-minute exercise sessions twice-weekly, for 3-months (24 total sessions). The control group maintained normal physical activity. People who had pulmonary rehabilitation maintained significantly higher levels of physical activity throughout the 3-month programme compared with control. Quality of life scores improved in the rehabilitation group whereas in the control group they worsened. After the 3-month follow-up period,	GDG feedback highlighted a Cochrane review[3] of 5 studies (n=168) of pulmonary rehabilitation in interstitial lung disease including a subgroup analysis in people with IPF, although the number of participants with IPF was not reported in the abstract. In people with IPF, pulmonary rehabilitation was associated with an increase in 6-minute walk test, improved oxygen consumption and reduced dyspnoea. Quality of life in people with IPF improved after pulmonary rehabilitation. No adverse effects of pulmonary rehabilitation were reported. The authors rated the quality	This evidence is unlikely to affect recommendations in CG163. The new Cochrane review evidence showed slightly greater improvements in outcomes than the guideline, which strengthens current recommendations. The guideline recommends offering pulmonary rehabilitation (1.5.1 to 1.5.4) if assessment shows it is appropriate. The RCTs also provided additional evidence in favour of pulmonary rehabilitation and the finding that effects did not persist in the 3 months after the programme is consistent with the

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self-reported physical activity levels in the rehabilitation group had reduced substantially and were not significantly different from the control group. Dyspnoea after 6-min walk tests did not change significantly between groups. In an RCT[2] (n=32), people with IPF were allocated either to pulmonary rehabilitation, consisting of 60-min supervised programme twice-weekly for 12 weeks, or to regular medical treatment alone. Cardiopulmonary exercise test, 6-min walking distance (6MWD) test, 30-second chair-stand test, pulmonary function tests, dyspnoea and QOL were assessed at baseline and at the end of the 12-week intervention. The pulmonary rehabilitation group had significantly higher 6-minute walk test scores, VO2 peak, work rate, anaerobic threshold, and forced vital capacity compared with usual care. Dyspnoea, quality of life and 30-second chair-stand were also significantly improved with pulmonary rehabilitation.	of evidence as low to moderate because of inadequate reporting of methods and small numbers of included participants. Little evidence was available about longer-term effects of pulmonary rehabilitation.	recommendation to repeat the assessment for pulmonary rehabilitation at 6-month or 12-month intervals (1.5.2).
163 – 10 What is the optimal course content, setting and duration for people referred for pulmonary rehabilitation programmes? (1.5.1–1.5.4)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Management – best supportive care		
163 – 11 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 people with IPF? (1.5.5–1.5.10)		
A cross-over RCT[4] (n=20) assessing ambulatory oxygen versus ambulatory air enrolled patients with IPF who had a partial pressure of arterial oxygen (PaO2) between 60 mm Hg and 80 mm Hg at rest, and desaturation of 88% or less in a room-air 6-minute walk test. Participants had forced vital capacity of 71.0% predicted, diffusion capacity for	None identified relevant to this question.	This evidence is unlikely to impact on CG163. The new evidence suggests that ambulatory oxygen does not differ from ambulatory air for the outcome of dyspnoea in patients with IPF who do not have hypoxaemia at rest. CG163 recommends ambulatory oxygen for relief of the symptom breathlessness (1.5.6, 1.5.7) and acknowledged

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carbon monoxide of 57.0% and PaO2 of 72.5 mmHg. Patients underwent a standardised 6-minute walk test and a 6-minute free walk test under each ambulatory gas. Oxygen and air were provided intranasally at a rate of 4 litres/minute. Dyspnoea was evaluated immediately, and at 1 minute and 2 minutes after the tests. No significant differences in dyspnoea were observed between ambulatory oxygen and air at each time point.		that breathlessness may be due to multiple factors including hypoxia, co-existing COPD or pulmonary hypertension and deconditioning. The new evidence provides information on dyspnoea only, without considering breathlessness as a symptom or quality of life.
Management – pharmacological interventions		
163 – 12 Which drug should be initiated first, for how long, and in what combination in the treatment of IPF? (1.5.11–1.5.15) What is the clinical and cost effectiveness of pharmacological interventions to manage patients with suspected or confirmed IPF: ambrisentan; azathioprine; bosentan; co-trimoxazole; mycophenolate mofetil; N-acetylcysteine; prednisolone; pharmacological interventions; IPF; proton-pump inhibitors; sildenafil; warfarin; combinations: prednisolone + azathioprine and prednisolone + azathioprine + N-acetylcysteine		
N-acetylcysteine In an RCT[5] (PANTHER), patients with IPF and mild-to-moderate impairment in pulmonary function were randomly assigned to receive a three-drug regimen of prednisone, azathioprine, and N-acetylcysteine; N-acetylcysteine alone; or placebo. Safety concerns associated with the 3-drug regimen meant that this arm of the trial stopped. The trial continued as a 2-group study (acetylcysteine versus placebo) without other changes; 133 and 131 patients were enrolled in the acetylcysteine and placebo groups, respectively. At 60 weeks, there was no significant difference in the primary outcome, change in forced vital capacity, between the acetylcysteine group and the placebo group (−0.18 litres and −0.19 litres, respectively). In addition, there were no significant differences between the acetylcysteine group and the placebo group in rates of	**Health Technology Assessment** GDG feedback highlighted a Health Technology Assessment[13] that systematically reviewed the clinical effectiveness (14 studies) and analysed the cost-effectiveness of treatments for IPF. A narrative review with meta-analysis and network meta-analysis was performed. A decision-analytic Markov model was developed to estimate cost-effectiveness of drug treatments for IPF. The systematic review included studies of azathioprine, N-acetylcysteine (alone or in combination), pirfenidone, nintedanib, sildenafil, thalidomide, pulmonary rehabilitation, and a disease management programme. Study quality was generally good, with a low risk of bias. Few interventions had any statistically significant effect on IPF and a lack of studies on palliative care approaches was identified. The current evidence suggests that some treatments appear to	**N-acetylcysteine** This evidence is unlikely to impact on recommendations in CG163. The new evidence suggests that N-acetylcysteine is no more effective than placebo, and the new study includes a substantially larger number of patients (n=264) than the evidence base used to develop the recommendation (2 studies, n=90). CG163 recommends (1.5.13) 'advise the person that oral N-acetylcysteine is used for managing IPF, but its benefits are uncertain'. CG163 considered early evidence from the PANTHER trial that suggested that N-acetylcysteine was 'relatively safe in therapeutic doses'. However, because the recommendation already acknowledges uncertainty about the benefits of this drug, and no new safety concerns have been raised about it use, there is no urgent need to review this recommendation.

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
death (4.9% versus 2.5%, p=0.30) or acute exacerbation (2.3% in each group, p>0.99). **Antibiotic treatment** In an RCT[6], patients with acute exacerbations of IPF were randomly assigned to antibiotic use guided by a procalcitonin threshold of 0.25 ng/ml or to standard practice. Clinical outcomes were assessed at baseline and at 30 days. Administering antibiotics based on procalcitonin levels resulted in lower duration of antibiotic treatment compared with standard practice. This was reported to be a significant reduction in the procalcitonin threshold group, but the p value was not reported in the abstract. Fewer patients received antibiotics in the procalcitonin threshold group compared with the control group. Treatment success, mortality rate, days in hospital and ventilation therapy were reported to be similar between the two groups. **Sildenafil** In a sub-analysis of a US RCT[7], evaluating sildenafil in people with IPF, 119 of 180 participants who had echocardiograms available were included. Echocardiograms were independently reviewed by 2 cardiologists. The prevalence of right ventricular hypertrophy was 12.8%, and prevalence of right ventricular systolic dysfunction was 18.6%. Right ventricular systolic pressure could be measured in 71 of the 119 participants in the sub-analysis (mean 42.5 mmHg). Multivariable regression analysis indicated that in people with right ventricular systolic dysfunction, those treated with sildenafil had less decrement in the 6-minute walk test and greater improvement in quality of life (St. George's Respiratory Questionnaire and EuroQol) than those on placebo.	be clinically effective. The model base-case results showed increased survival for 5 drug treatments compared with best supportive care. General recommendations about cost-effectiveness could not be made owing to limitations in the evidence base.	This area will be examined again at the next surveillance review of the guideline. **Antibiotic treatment** This evidence is unlikely to impact on recommendations in CG163. The new evidence suggests that antibiotic use for IPF exacerbations can be reduced by prescribing on the basis of procalcitonin levels. NICECG163 currently has no specific recommendations for use of antibiotics in IPF. Recommendation 1.5.15 notes: 'Manage any comorbidities according to best practice.' The new evidence is unlikely to affect standard care in treating respiratory infections because the study abstract did not give information about the methods used as standard practice for diagnosis of respiratory infection. **Sildenafil** This evidence is unlikely to affect recommendations in CG163. The new evidence suggests that sildenafil may be more effective than placebo in a subset of people with IPF and right ventricular systolic dysfunction. It is a post-hoc subanalysis of the STEP-IPF study that was considered in CG163. In the overall study population the effect on 6-minute walk test was not significant. CG163 says 'do not use…' sildenafil (1.5.12), and this recommendation was made because the benefit of sildenafil was thought to be uncertain due to inconsistent effects across outcome measures, including worsening of some outcomes such as the 6-minute walk test, and adverse events such as hypotension, oedema and visual

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Ambrisentan In an RCT[8], patients with IPF aged 40–80 years with minimal or no honeycombing on high-resolution computed tomography scans were randomly assigned to ambrisentan, 10 mg/day, or placebo. The primary end point was time to disease progression, defined as death, respiratory hospitalisation, or a categorical decrease in lung function. The study was terminated after enrolment of 492 patients (75% of intended enrolment) because an interim analysis showed that ambrisentan was associated with increased disease progression (27.4% of patients) compared with the placebo group (17.2% of patients; p=0.010). Ambrisentan was also associated with greater decline in lung function (p=0.109) and respiratory hospitalisation (p=0.007) compared with placebo. Rates of death and pulmonary hypertension did not differ between groups. **Co-trimoxazole** An economic evaluation[9] based on the results of an RCT trial (n=181) of co-trimoxazole 960 mg daily in people older than 40 years with fibrotic idiopathic interstitial pneumonia suggested that co-trimoxazole had a mean cost per patient of £1177 compared with placebo. Mean quality-adjusted life years (QALYs) were 0.053 higher in the co-trimoxazole group, resulting in an incremental cost-effectiveness ratio of £22,012 per QALY gained with a 54% probability of being below £30,000. **Pirfenidone** An RCT[10] was identified that assessed the use of pirfenidone in people with IPF. CG163 directed readers to		disturbances. The new evidence is unlikely to impact on guidance because it is a post-hoc subanalysis of a trial that found no benefit of sildenafil. **Ambrisentan** This evidence is unlikely to impact on CG163. CG163 includes ambrisentan in a list of 'do not use' drugs (1.5.12). This recommendation was made on the basis of a conference abstract that reported the results of this trial; however, the full results have now been published in a journal and considered as part of this 2-year surveillance review. **Co-trimoxazole** This new evidence is unlikely to impact on CG163. The new evidence suggests that co-trimoxazole may be cost effective at a threshold of £30,000. However, CG163 recommends against the use of co-trimoxazole, based mainly on evidence from the RCT on which this economic analysis was based. The findings of this economic analysis are unlikely to affect this recommendation because the RCT did not find significant differences between co-trimoxazole and placebo for any outcomes in intention-to-treat analyses. **Pirfenidone** The new evidence is unlikely to have an impact on CG163. A recommendation in CG163 refers readers to Pirfenidone for the treatment of idiopathic pulmonary fibrosis (NICE TA282), which recommends pirfenidone in a narrower population than the marketing authorisation. The new evidence may be considered in the scheduled update of TA282 (publication expected May 2016).

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
Pirfenidone for treating idiopathic pulmonary fibrosis, NICE TA282 (now being updated), which makes recommendations about use of this drug. This information will be passed to the TA team for consideration when the topic undergoes the review proposal process. **Nintedanib** Although a relevant study[11] about nintedanib was identified, NICE is developing the technology appraisal Idiopathic pulmonary fibrosis – nintedanib. This information will be passed to the TA team for consideration. **Macitentan** In a phase II RCT[12] (n=178), adults with IPF of <3 years duration and a histological pattern of usual interstitial pneumonia on surgical lung biopsy were randomised (2:1) to macitentan 10 mg once-daily (n=119) or placebo (n=59). The median change from baseline up to month 12 in forced vital capacity was −0.20 litres in the macitentan arm and −0.20 litres in the placebo arm. Overall, no differences between treatments were observed in pulmonary function tests or time to disease worsening or death.		This information will be passed onto the TA team for consideration when this topic undergoes the review proposal process. **Nintedanib** This evidence is unlikely to impact on CG163. Nintedanib is currently undergoing a NICE technology appraisal, with publication expected in January 2016. **Macitentan** This evidence is unlikely to impact on CG163. The evidence suggests that macitentan had no effect on IPF. CG163 does not contain recommendations on macitentan in IPF; macitentan does not have a UK marketing authorisation for this indication and the manufacturer ceased further development for this indication on the basis of these results. **Health Technology Assessment** The new evidence is unlikely to impact on CG163. The authors reported in the abstract that few interventions had any statistically significant effect on IPF and indicated that further research is required into the effects of symptom control interventions. As such, no conclusive data was reported on pharmacological interventions which would impact on the current recommendations in this area.
163 – 13 Which measures can be taken to minimise the occurrence/severity of adverse events when undergoing pharmacological treatment for IPF? (1.5.11–1.5.15)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Management – lung transplantation		

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
163 – 14 What is the optimal timing to consider a patient with IPF for lung transplantation referral? (1.5.16, 1.5.17)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Management – ventilation		
163 – 15 In acute or acute-on chronic respiratory failure in patients with IPF, what is the value of non-invasive and invasive ventilation? (1.5.18, 1.5.19)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Review and follow-up		
163 – 16 How often should a patient with confirmed diagnosis of IPF be reviewed? (1.6.1, 1.6.2)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
163 – 17 In which healthcare setting and by whom should a review appointment for patients with confirmed IPF be conducted? (1.6.1, 1.6.2)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
Research recommendations		
RR – 01 What is the value of bronchoalveolar lavage in people in whom IPF is considered the most likely diagnosis when clinical and CT findings are insufficient to support a confident diagnosis?		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.
RR – 02 What is the value of surgical lung biopsy in people in whom IPF is considered the most likely diagnosis when clinical and computed tomography findings are insufficient to support a confident diagnosis?		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
RR – 03 What is the value of transthoracic echocardiography in detecting pulmonary hypertension and determining prognosis in people with IPF?		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.
RR – 04 What is the agreement between radiologists in the interpretation of CT in patients with suspected IPF?		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.
RR – 05 What is the feasibility of a formal 'CT scoring system' to assess disease severity in patients with suspected IPF?		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.
RR – 06 What is the utility of a formal CT scoring system in determining outcome in patients with suspected IPF?		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.
RR – 07 Does pulmonary rehabilitation improve outcomes for patients with IPF?		
See CG163–08 for new evidence.	See CG163-08 for new evidence identified by topic experts	Although new evidence was identified, the size of studies is not substantially larger than the previous evidence base so this research recommendation is not likely to have been answered at this time.
RR – 08 Does nocturnal oxygen improve outcomes in IPF?		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.
RR – 09 Does ambulatory oxygen improve outcomes in IPF?		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.
RR – 10 Does short-burst oxygen therapy improve outcomes in IPF?		
See CG163–10 for new evidence	None identified relevant to this question.	Although a new study was identified, it was very small (n=20) so would be unlikely to answer this question at this time.

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
RR – 11 What is the value of pharmacological treatments of cough in IPF?		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.
RR – 12 Is anti-reflux therapy an effective treatment for IPF?		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.
RR – 13 Is corticosteroid therapy an effective treatment for IPF?		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect this research recommendation.
RR – 14 Is co-trimoxazole an effective treatment for IPF?		
See CG163–13 for new evidence.	None identified relevant to this question.	Although a new study of co-trimoxazole was identified, it was a cost-effectiveness analysis based on a study already considered in developing the guideline so adds no new information.

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