National Institute for Health and Care Excellence

Surveillance programme

Surveillance proposal consultation document

Idiopathic pulmonary fibrosis in adults: diagnosis and management NICE guideline CG163 – 4-year surveillance review

Background information

Guideline issue date: June 2013

2-year surveillance review: no update

Surveillance proposal for consultation

We will not update the guideline at this time.

We also propose to remove the following NICE research recommendations from the NICE version of the guideline and the NICE research recommendations database:

- RR–01 What is the value of bronchoalveolar lavage in people in whom idiopathic pulmonary fibrosis is considered the most likely diagnosis when clinical and CT findings are insufficient to support a confident diagnosis?
- RR–02 What is the value of surgical lung biopsy in people in whom idiopathic pulmonary fibrosis is considered the most likely diagnosis when clinical and CT findings are insufficient to support a confident diagnosis?
- RR–03 Does pulmonary rehabilitation improve outcomes for people with idiopathic pulmonary fibrosis?
- RR–04 Does ambulatory oxygen improve outcomes in idiopathic pulmonary fibrosis?

- RR–05 Is anti-reflux therapy an effective treatment for idiopathic pulmonary fibrosis?

Reason for the proposal

New evidence

We found 24 new studies in a search for randomised controlled trials and systematic reviews published between 13 February 2015 and 22 September 2016. We also considered 2 additional studies identified by members of the guideline committee who originally worked on this guideline.

Evidence identified in previous surveillance 2 years after publication of the guideline was also considered. This included 12 studies identified by search.

From all sources, 38 studies were considered to be relevant to the guideline.

This included new evidence that is consistent with current recommendation:

- diagnosis
- information and support
- pulmonary rehabilitation
- best supportive care.

We also identified new evidence in the following areas that was inconsistent with, or not covered by, current recommendations, but the evidence was not considered to impact on the guideline at this time:

- pharmacological interventions.

We did not find any new evidence on:

- awareness of clinical features of idiopathic pulmonary fibrosis
- prognosis
- lung transplantation
- ventilation
- review and follow-up.

None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations. We asked topic experts whether they agreed with this proposal. Generally, the topic experts thought that an update was not needed.

No equalities issues were identified during the surveillance process.

Research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. See the research recommendations section for further information.

For this surveillance review we assessed 5 prioritised research recommendations, and proposed that all 5 should be removed from the NICE version of the guideline and the NICE database.

Overall decision

After considering all the new evidence and views of topic experts, we decided not to update this guideline.

We also propose to remove 5 NICE research recommendations from the NICE version of the guideline and the NICE research recommendations database.

Further information

See appendix A: summary of new evidence from surveillance below for further information.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

Appendix A: Summary of new evidence from surveillance

Awareness of clinical features of idiopathic pulmonary fibrosis

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?

Recommendations derived from this question

1.1.1 Be aware of idiopathic pulmonary fibrosis when assessing a patient with the clinical features listed below and when considering requesting a chest X-ray or referring to a specialist:

- age over 45 years
- persistent breathlessness on exertion
- persistent cough
- bilateral inspiratory crackles when listening to the chest
- clubbing of the fingers
- normal spirometry or impaired spirometry usually with a restrictive pattern but sometimes with an obstructive pattern

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Diagnosis

163 – 02 In suspected IPF what is the value of adding biopsy to clinical evaluation, PFTs, CT +/- bronchoalveolar lavage for confirming the diagnosis of IPF?

Recommendations derived from this question

1.2.1 Assess everyone with suspected idiopathic pulmonary fibrosis by:

- taking a detailed history, carrying out a clinical examination (see recommendation1.1.1 for clinical features) and performing blood tests to help exclude alternative diagnoses, including lung diseases associated with environmental and occupational exposure, with connective tissue diseases and with drugs **and**
- performing lung function testing (spirometry and gas transfer) **and**
- reviewing results of chest X-ray **and**
- performing CT of the thorax (including high-resolution images).

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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163 – 03 In suspected IPF what is the value of adding multidisciplinary team (MDT) consensus to clinical assessment, PFTs and CT in the diagnosis of IPF?

Recommendations derived from this question

1.2.2 Diagnose idiopathic pulmonary fibrosis only with the consensus of the multidisciplinary team (listed in table1), based on:

- the clinical features, lung function and radiological findings (see recommendation1.2.1)
- pathology when indicated (see recommendation1.2.4).

1.2.3 At each stage of the diagnostic care pathway the multidisciplinary team should consist of a minimum of the healthcare professionals listed in table 1, all of whom should have expertise in interstitial lung disease

Table 1- Minimum composition of multidisciplinary team involved in diagnosing idiopathic pulmonary fibrosis

Stage of diagnostic care pathway	Multidisciplinary team composition (all healthcare professionals should have expertise in interstitial lung disease)
After clinical evaluation, baseline lung function and CT	Consultant respiratory physician Consultant radiologist Interstitial lung disease specialist nurse Multidisciplinary team coordinator
When considering performing bronchoalveolar lavage, and/or transbronchial biopsy or surgical lung biopsy Only some patients will have bronchoalveolar lavage or transbronchial biopsy but they may be being considered for surgical lung biopsy	Consultant respiratory physician Consultant radiologist Consultant histopathologist Thoracic surgeon as appropriate Interstitial lung disease specialist nurse Multidisciplinary team coordinator
When considering results of bronchoalveolar lavage, transbronchial biopsy or surgical lung biopsy	Consultant respiratory physician Consultant radiologist Consultant histopathologist Interstitial lung disease specialist nurse Multidisciplinary team coordinator
See chapter 6.5 (Multidisciplinary Team) in full guideline for more information on the expertise of the multidisciplinary team.	

1.2.4 If the multidisciplinary team cannot make a confident diagnosis from clinical features, lung function and radiological findings, consider:

- bronchoalveolar lavage or transbronchial biopsy and/or
- surgical lung biopsy, with the agreement of the thoracic surgeon.

1.2.5 Discuss with the person who may have idiopathic pulmonary fibrosis:

- the potential benefits of having a confident diagnosis compared with the uncertainty of not having a confident diagnosis **and**
- the increased likelihood of obtaining a confident diagnosis with surgical biopsy compared with bronchoalveolar lavage or transbronchial biopsy **and**
- the increased risks of surgical biopsy compared with bronchoalveolar lavage or transbronchial biopsy.

1.2.6 When considering bronchoalveolar lavage, transbronchial biopsy or surgical lung biopsy take into account:

- the likely differential diagnoses **and**
- the person's clinical condition, including any comorbidities.

1.2.7 If a confident diagnosis cannot be made continue to review the person under specialist care.

Surveillance decision

This review question should not be updated.

Diagnosis

2-year surveillance summary

No relevant evidence was identified.

4-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

One topic expert indicated that the original guidance suggested access to expert chest radiologist and this needs reinforcing with the recent studies**.** A cohort study [1] that evaluated inter-multidisciplinary team agreement for the diagnosis of diffuse parenchymal lung disease was highlighted by a topic expert. The study was a multicentre evaluation of clinical data of patients who presented to the interstitial lung disease unit of two NHS Foundation Trusts in the UK and required multidisciplinary team meeting (MDTM) characterisation. Seven MDTMs, consisting of at least one clinician, radiologist, and pathologist, from seven countries (Denmark, France, Italy, Japan, Netherlands, Portugal, and the UK) evaluated cases of diffuse parenchymal lung disease in a two-stage process. The clinician, radiologist, and pathologist independently evaluated each case, selected up to five differential diagnoses from a choice of diffuse lung diseases, and chose likelihoods for each of their differential diagnoses, without inter-disciplinary consultation. Second, these specialists reviewed all data at an MDTM, selected up to five differential diagnoses, and chose diagnosis likelihoods. The findings indicated that agreement between MDTMs for diagnosis in diffuse lung disease was acceptable and good for a diagnosis of idiopathic pulmonary fibrosis (IPF). That was validated by the non-significant greater prognostic separation of an IPF diagnosis made by MDTMs than the separation of a diagnosis made by individual clinicians or radiologists. Likewise, MDTMs made the diagnosis of IPF with higher confidence and more frequently than did clinicians or radiologists. The authors concluded that this difference is of particular importance, because accurate and consistent diagnoses of IPF are needed if clinical outcomes are to be optimised.

Impact statement

The new evidence is consistent with CG163 recommendation that suggests diagnosing IPF only with the consensus of the multidisciplinary team based on the clinical features, lung function and radiological findings and pathology. CG163 recommended having a consultant radiologist in the multidisciplinary team at all stage of IPF diagnostic care pathway.

New evidence is unlikely to change guideline recommendations.

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163 – 04 How and by whom is a MDT diagnostic consensus best achieved (i.e. constituency of the MDT, specialist clinics, networks)?

Recommendations derived from this question

The same recommendations were derived from this question as in 163-03.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Information and support

163 – 05 What is the specific type of psychosocial support and information that should be provided for patients diagnosed with IPF?

Recommendations derived from this question

1.3.1 The consultant respiratory physician or interstitial lung disease specialist nurse should provide accurate and clear information (verbal and written) to people with idiopathic pulmonary fibrosis, and their families and carers with the person's consent. This should include information about investigations, diagnosis and management.

1.3.2 NICE has produced guidance on the components of good patient experience in adult NHS services. Follow the recommendations in Patient experience in adult NHS services (NICE clinical guideline 138).

1.3.3 An interstitial lung disease specialist nurse should be available at all stages of the care pathway to provide information and support to people with idiopathic pulmonary fibrosis and their families and carers with the person's consent.

1.3.4 Offer advice, support and treatment to aid smoking cessation to all people with idiopathic pulmonary fibrosis who also smoke, in line with Smoking cessation services (NICE public health guidance 10).

Surveillance decision

This review question should not be updated.

Information and support

2-year surveillance summary

No relevant evidence was identified.

4-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

One topic expert indicated that since the NICE guideline was published there has been a service specification written by NHS England Specialised Respiratory Clinical Reference Group which lays down a multi-stage approach to treatment where diagnosis is performed by a specialist centre but treatment is delivered locally by district general hospitals and by GPs. Another topic expert specified that there is IPF charter issued by British Lung Foundation. A multi-centre mixed-methods study [2] that recruited participants with IPF at four stages of the disease was highlighted by a topic expert. Qualitative analysis was used to analyse 48 semi-structured interviews with 27 patients and

paired carers. Four key elements that had significant impact on their care experience were outlined by patients and carers. The four factors were 'focus of clinical encounters', 'timely identification of changes in health status and functional activity',' understanding of symptoms and medical interventions' and 'coping strategies and carer roles'. The authors concluded that patients diagnosed with IPF have a clear understanding of their prognosis but little understanding of how their disease will progress and how it will be managed.

Impact statement

The new evidence indicates that support is needed for patients and carers at key transition points. This is in line with CG163 that recommends 'an interstitial lung disease specialist nurse should be available at all stages of the care pathway to provide information and support to people with idiopathic pulmonary fibrosis and their families and carers with the person's consent' (1.3.3).

Topic experts felt that service delivery (i.e. commissioning) has changed since the last guideline. They highlighted service specification written by NHS England Specialised Respiratory Clinical Reference Group and IPF charter issued by British Lung Foundation. The current recommendations may need to cross refer to the new service specifications highlighted by NHS England.

New evidence is unlikely to change guideline recommendations.

Prognosis

163 – 06 Do serial pulmonary function tests (PFTs) (resting spirometric, gas transfer measurement and oxygen saturation) predict prognosis of IPF?

Recommendations derived from this question

1.4.1 Measure the initial rate of decline in the person's condition, which may predict subsequent prognosis, by using lung function test results (spirometry and gas transfer) at:

- diagnosis **and**
- 6 months and 12 months after diagnosis. Repeat the lung function tests at shorter intervals if there is concern that the person's condition is deteriorating rapidly.

1.4.2 Discuss prognosis with people with idiopathic pulmonary fibrosis in a sensitive manner and include information on:

- the severity of the person's disease and average life expectancy
- the varying courses of disease and range of survival
- management options available.

1.4.3 Do not use the 6-minute walk distance at diagnosis to estimate prognosis. (The 6-minute walk test may be useful for other purposes, see recommendation1.5.1.)

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

163 – 07 Does baseline sub-maximal exercise testing predict prognosis of IPF?

Recommendations derived from this question

The same recommendations were derived from this question as in CG136-06.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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163 – 08 Does baseline echocardiography predict prognosis of IPF?

Recommendations derived from this question

The same recommendations were derived from this question as in CG136-06.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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163 – 09 Do baseline CT scores predict prognosis of IPF?

Recommendations derived from this question

The same recommendations were derived from this question as in CG136-06.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Management - Pulmonary rehabilitation

163 – 10 What are the benefits of pulmonary rehabilitation programmes for people with confirmed IPF?

Recommendations derived from this question

1.5.1 Assess people with idiopathic pulmonary fibrosis for pulmonary rehabilitation at the time of diagnosis. Assessment may include a 6-minute walk test (distance walked and oxygen saturation measured by pulse oximetry) and a quality-of-life assessment.

1.5.2 Repeat the assessment for pulmonary rehabilitation for people with idiopathic pulmonary fibrosis at 6-month or 12-month intervals.

1.5.3 If appropriate after each assessment, offer pulmonary rehabilitation including exercise and educational components tailored to the needs of people with idiopathic pulmonary fibrosis in general.

1.5.4 Pulmonary rehabilitation should be tailored to the individual needs of each person with idiopathic pulmonary fibrosis. Sessions should be held somewhere that is easy for people with idiopathic pulmonary fibrosis to get to and has good access for people with disabilities.

Surveillance decision

This review question should not be updated.

Pulmonary rehabilitation

2-year surveillance summary

A Cochrane review [3] of 5 studies (n=168) of pulmonary rehabilitation in interstitial lung disease including a subgroup analysis in people with IPF was identified. 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 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.

In an RCT[4], 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, 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[5] (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, work rate, anaerobic threshold, and forced vital capacity (FVC) compared with usual care. Dyspnoea, quality of life and 30-second chair-stand were also significantly improved with pulmonary rehabilitation.

4-year surveillance summary

Two studies [6,7]derived from one RCT were identified that evaluated the long-term effects of

a 12 weeks exercise trainings (ET) on clinical outcomes and short-term Improvement in physical activity and body composition in patients with IPF.

The first study [6] examined the effect of participating in a 12-week supervised ET programme on physical activity and body composition in patients with IPF. The main outcome was the changes in physical activity levels that measured by the International Physical Activity Questionnaire. The findings indicated that the physical activity and body composition in patients with IPF were improved after a 12-week supervised ET programme, although the benefits were not sustained at 11-month follow-up. The authors concluded that these results might support the efficacy of participation in supervised ET to improve physical activity and body composition in patients with IPF; however, maintenance strategies are needed to preserve the improved outcomes.

The second study [7] evaluated the long-term effects of the 12 weeks ET on clinical outcomes. Thirty-four patients with IPF were randomly allocated to ET (n=14) or control groups (n=14). ET group participated in a 12-week supervised exercise programme, while the control group continued with regular medical treatment alone. Exercise capacity, 30 s-chair-stand test for leg strength, dyspnea, and Saint George's Respiratory Questionnaire (SGRQ) for quality of life (QOL) were assessed at baseline and re-evaluated at 11 months from baseline. In addition, the impact of the 12-week intervention was analysed with respect to survival and cardio-respiratory-related hospitalisations at 30-month time point from baseline. At 11-month follow-up, the ET programme showed that clinical outcomes were preserved at baseline levels with some maintenance of improvements in leg strength and QOL in the ET group. The control group showed a trend of deterioration in the outcomes. At 30 months, the ET programme did not show benefits in prognosis. The authors concluded that ET should be included as a long-term continued treatment and as a core component of pulmonary rehabilitation programmes for IPF patients.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The 2-year surveillance review found slightly greater improvements in outcomes than the guideline, which strengthens current recommendations. The evidence was in favour of pulmonary rehabilitation which is currently recommended.

Evidence from 4-year surveillance suggests that 12 weeks ET has improved clinical outcomes and body composition in patients with IPF. That is supported by the current recommendation that indicates to offer pulmonary rehabilitation including exercise and educational components tailored to the needs of people with IPF in general. Therefore this evidence is unlikely to affect recommendations in CG163.

New evidence is unlikely to change guideline recommendations.

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163 – 11 What is the optimal course content, setting and duration for people referred for pulmonary rehabilitation programmes?

Recommendations derived from this question

The same recommendations were derived from this question as in 136-10.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Management – best supportive care

163 – 12 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?

Recommendations derived from this question

1.5.5 Offer best supportive care to people with idiopathic pulmonary fibrosis from the point of diagnosis. Best supportive care should be tailored to disease severity, rate of progression, and the person's preference, and should include if appropriate:

- information and support (see recommendation 1.3.1)
- symptom relief
- management of comorbidities
- withdrawal of therapies suspected to be ineffective or causing harm
- end of life care.

1.5.6 If the person is breathless on exertion consider assessment for:

- the causes of breathlessness and degree of hypoxia **and**
- ambulatory oxygen therapy and long-term oxygen therapy **and/or**
- pulmonary rehabilitation.

1.5.7 If the person is breathless at rest consider:

- assessment for the causes of breathlessness and degree of hypoxia **and**
- assessment for additional ambulatory oxygen therapy and long-term oxygen therapy **and**
- the person's psychosocial needs and offering referral to relevant services such as palliative care services **and**
- pharmacological symptom relief with benzodiazepines and/or opioids.

1.5.8 Assess the oxygen needs of people who have been hospitalised with idiopathic pulmonary fibrosis before they are discharged.

1.5.9 If the person has a cough consider:

- treatment for causes other than idiopathic pulmonary fibrosis (such as gastro-oesophageal reflux disease, post-nasal drip)
- treating with opioids if the cough is debilitating
- discussing treatment with thalidomide* with a consultant respiratory physician with expertise in interstitial lung disease if the cough is intractable.

1.5.10 Ensure people with idiopathic pulmonary fibrosis, and their families and carers, have access to the full range of services offered by palliative care teams. Ensure there is collaboration between the healthcare professionals involved in the person's care, community services and the palliative care team.

* At the time of publication (June 2013), thalidomide did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

Surveillance decision

This review question should not be updated.

Best supportive care

2-year surveillance summary

A cross-over RCT[8] (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 FVC of 71.0% predicted, diffusion capacity for 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.

4-year surveillance summary

A systematic review[9] was identified that examined the effects of ambulatory and short-burst oxygen therapy, separately, on exercise capacity, dyspnoea and quality of life in people who have interstitial lung disease, particularly those with IPF. Three studies with n=98 participants with IPF included. Two studies did not demonstrate any beneficial effect of supplemental oxygen on exercise capacity or exertional dyspnoea. One study showed an increase in exercise capacity as assessed by endurance time with supplemental oxygen. The authors concluded that no evidence found to support or contradict the use of ambulatory or short burst oxygen in interstitial lung disease due to the limited available evidence.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

This evidence is unlikely to impact on CG163.

The 2-year surveillance review found 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.

Evidence from 4-year surveillance does not support the use of ambulatory or short burst oxygen in interstitial lung disease.

CG163 recommends ambulatory oxygen for relief of the symptom breathlessness (1.5.6, 1.5.7) and acknowledged that breathlessness may be due to multiple factors including hypoxia, co-existing COPD or pulmonary hypertension and deconditioning. The new evidence is broadly in line with current recommendations.

New evidence is unlikely to change guideline recommendations.

Management - disease-modifying pharmacological interventions

163 – 13 Which drug should be initiated first, for how long, and in what combination in the treatment of IPF?

Subquestion

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
- IPF; proton-pump inhibitors
- Sildenafil
- warfarin
- combinations:
  - prednisolone + azathioprine and
  - prednisolone + azathioprine + N-acetylcysteine?

Recommendations derived from this question

1.5.11 For guidance on pirfenidone for the management of idiopathic pulmonary fibrosis, refer to Pirfenidone for the treatment of idiopathic pulmonary fibrosis (NICE technology appraisal guidance 282).

1.5.12 Do not use any of the drugs below, either alone or in combination, to modify disease progression in idiopathic pulmonary fibrosis:

- ambrisentan
- azathioprine
- bosentan
- co-trimoxazole
- mycophenolate mofetil
- prednisolone
- sildenafil
- warfarin

1.5.13 Advise the person that oral N-acetylcysteine** is used for managing idiopathic pulmonary fibrosis, but its benefits are uncertain.

1.5.14 If people with idiopathic pulmonary fibrosis are already using prednisolone or azathioprine, discuss the potential risks and benefits of discontinuing, continuing or altering therapy.

1.5.15 Manage any comorbidities according to best practice. For gastro-oesophageal reflux disease, see Managing dyspepsia in adults in primary care (NICE clinical guideline 17).

** At the time of publication (June 2013), N-acetylcysteine did not have a UK marketing authorisation. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information

Surveillance decision

This review question should not be updated.

Cross referral will be made to NICE TA282 and NICE TA379.

Pharmacological interventions

2-year surveillance summary

Ambrisentan

In an RCT[10], 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.

Antibiotic treatment

In an RCT[11], 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 was reported to be similar between the two groups.

An economic evaluation[12] 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.

N-acetylcysteine

In an RCT[13] (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 (N-acetylcysteine versus placebo) without other changes; 133 and 131 patients were enrolled in the N-acetylcysteine and placebo groups, respectively. At 60 weeks, there was no significant difference in the primary outcome, change in FVC, between the N-acetylcysteine group and the placebo group (−0.18 litres and −0.19 litres, respectively). In addition, there were no significant differences between the N-acetylcysteine group and the placebo group in rates of death (4.9% versus 2.5%) or acute exacerbation (2.3% in each group).

Sildenafil

In a sub-analysis of a US RCT[14], 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 than those on placebo.

Pirfenidone

An RCT[15] was identified that assessed the use of pirfenidone in people with IPF. CG163 directed readers to Pirfenidone for treating IPF, NICE TA282 (now being updated), which makes recommendations about use of this drug. The information passed to the TA team for consideration when the topic undergoes the review proposal process.

Nintedanib

A relevant study[16] about nintedanib was identified. The information passed to the TA team as at the time of surveillance review, NICE was developing the technology appraisal on nintedanib for IPF.

Macitentan

In a phase II RCT[17] (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 FVC 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.

No relevant evidence was identified.

4-year surveillance summary

N-acetylcysteine

A systematic review [18] was identified that evaluated the efficacy of N-acetylcysteine, compared with control, for the treatment of IPF. Findings from meta-analysis of five trials, with a total of 564 patients, showed no beneficial effect of N- acetylcysteine on changes in FVC, changes in predicted carbon monoxide diffusing capacity, rates of adverse events, or death rates when compared with the control group. N-acetylcysteine was found to have a significant effect only on decreases in percentage of predicted vital capacity and 6 minutes walking test distance.

Pirfenidone

An integrated analysis of safety data [19] from five clinical trials was identified that evaluated safety outcomes of pirfenidone in patients with IPF. Data from all patients (n=1299) treated with pirfenidone in the three multinational phase 3 studies (CAPACITY, ASCEND and two ongoing open-label studies [RECAP]) were included in the analysis. Safety outcomes were assessed during the period from the first dose until 28 days after the last dose of study drug. The cumulative total exposure to pirfenidone was 3160 person exposure years (median duration of exposure was 1.7 years, range 1 week to 9.9 years). The side effects (gastrointestinal events, rash) were generally mild to moderate in severity and without significant clinical consequence. Overall findings indicated that long-term treatment with pirfenidone is safe and generally well tolerated.

Four post hoc analyses on data from patients randomised to pirfenidone or placebo in the ASCEND and CAPACITY studies (N = 1247) were identified.

The first post hoc analysis [20] investigated the efficacy of pirfenidone at 12 months in patients stratified by mild vs more pronounced restrictive disease as well as by GAP (assessment based on Gender, Age, and Physiology) stage. Efficacy outcomes were analysed at 12 months in all patients (n=1247) randomised to pirfenidone or placebo in the CAPACITY or ASCEND studies. The group stratified into two different sets of subgroups defined by dichotomisation of baseline FVC (≥80%, <80%) and GAP stage. The findings indicated that in the placebo population, clinically significant disease progression occurred in both subgroups with mild and more pronounced restrictive disease, underlying the need for early intervention. The magnitude of pirfenidone treatment effect on functional measures was comparable in both subgroups of patients, supporting the initiation of treatment soon after diagnosis, when pulmonary function is relatively preserved.

The second identified post hoc analysis [21] evaluated the most precise estimates of the magnitude of treatment effect with pirfenidone on measures of disease progression in patients with IPF. All patients (n=1247) randomised to pirfenidone or placebo in the CAPACITY or ASCEND studies were included in the analysis. At 1 year, pirfenidone reduced the proportion of patients with a >10% decline in per cent predicted, FVC or death by 43.8% and increased the proportion of patients with no decline by 59.3%. A treatment benefit was also observed for progression-free survival, 6-min walk distance and dyspnoea. Gastrointestinal and skin-related adverse events were more common in the pirfenidone group, but rarely led to discontinuation. Overall findings indicated that treatment with pirfenidone for 1 year resulted in clinically meaningful reductions in disease progression in patients with IPF.

The third identified post hoc analysis [22]evaluated the effect of continued pirfenidone treatment after 6 months in patients with IPF who were hospitalised due to any cause within the first 6 months of study treatment. The data included all patients randomised to pirfenidone or placebo in the ASCEND and CAPACITY studies (N = 1247). A total of 44/623 (7.1%) and 49/624 (7.9%) patients in the pooled pirfenidone and placebo groups, respectively, were hospitalised due to any cause within the first 6 months of treatment. FVC ≥10% or death was 4/623 (9.1%) in pirfenidone group and 16/624 (32.7%) in placebo group. The authors concluded that continued treatment with pirfenidone may be beneficial to patients with IPF who are hospitalised within the first 6 months of treatment.

The forth post hoc analysis [23] of the ASCEND and CAPACITY studies showed a significant reduction in the risk of all-cause mortality over 52 weeks in patients with IPF (total n=1247) treated with pirfenidone compared with placebo. Pooled outcome analysis showed a clear trend towards reduced risk of treatment emergent all-cause mortality in patients with

IPF treated with pirfenidone (27/623) compared with placebo (44/624).

A phase III clinical trial [24] of pirfenidone in patients with IPF was identified that examined the beneficial effect of pirfenidone on disease progression. A total of 555 patients with IPF were randomised to receive either oral pirfenidone or placebo for 52 weeks. The result showed that pirfenidone reduced the decline in the 6-minute walk distance and improved progression-free survival. There was no significant difference between- the two groups in dyspnoea scores or in rates of death from any cause or from IPF. However, the authors indicated that, death from any cause and from IPF favoured pirfenidone group. Gastrointestinal and skin-related adverse events were more common in the pirfenidone group than in the placebo group but rarely led to treatment discontinuation. The author concluded that pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival.

An extended analysis [25] of a clinical trial was identified that investigated the efficacy of pirfenidone with respect to severity of the disease in patients with IPF. The efficacy of pirfenidone for vital capacity and improved progression-free survival over 52 weeks was compared among the three sub-populations. The findings indicated that of 264 patients, 102 (39%), 90 (34%), and 72 patients (27%) were classified as having mild, moderate, and severe grades of functional impairment, respectively. This classification was associated with arterial oxygen partial pressure at rest and degree of dyspnea at baseline. While pirfenidone attenuated vital capacity decline at all grades of severity, covariance analysis revealed pirfenidone to have better efficacy in the sub-population with mild-grade IPF. Mixed model repeated measures analysis confirmed that pirfenidone markedly reduced vital capacity decline in patients with mild-grade IPF compared to its effects in patients with moderate or severe IPF. Pirfenidone also improved progression-free survival considerably in patients with mild-grade IPF. The authors concluded that pirfenidone exerted better therapeutic effects in patients with milder IPF. Further analysis with a larger population is needed to confirm these results.

Nintedanib

A meta-analysis of data from one phase II and 2 phase III trials [26] was identified that assessed the efficacy and safety of nintedanib versus placebo in patients with IPF. A total of 1231 patients (nintedanib n=723, placebo n=508) were included. Adjusted annual rate of decline in FVC was statistically significantly lower in placebo compared with nintedanib group. Adjusted mean change from baseline in St SGRQ score at week 52 was statistically significantly lower in nintedanib group compared to placebo group. Hazard ratios for time to all-cause and on-treatment mortality were 0.70 (not statistically significant) and 0.57 (statistically significant) in favour of nintedanib. Diarrhoea was the most frequent adverse event in the nintedanib group (61.5% versus 17.9% placebo). The overall findings indicated that nintedanib had a beneficial effect on slowing disease progression in patients with IPF.

A post-hoc subgroup analysis [27] from three trials was identified that assessed the effect of nintedanib in subgroups of patients with IPF by diagnostic criteria. Data from patients with honeycombing on high-resolution computed tomography (HRCT) and/or confirmation of usual interstitial pneumonia (UIP) by biopsy compared versus patients without either, using pooled data from the INPULSIS trials. 723 (68.1%) patients had honeycombing and/or biopsy and 338 (31.9%) had no honeycombing or biopsy. The overall findings indicated that the patients with IPF diagnosed in clinical practice who have possible UIP with traction bronchiectasis on HRCT with no biopsy have disease that progresses in a similar way, and responds similarly to nintedanib, as patients with honeycombing on HRCT and/or confirmation of UIP by biopsy.

Another post-hoc subgroup analysis [28] of pooled data from the INPULSIS trials was identified that investigated the impact of baseline lung function impairment (FVC >80% versus ≤80% predicted) on the effect of nintedanib . 485 patients (nintedanib 295, placebo 190) had FVC >80% predicted and 576 patients (nintedanib 343, placebo 233) had FVC ≤80% predicted. The findings showed that nintedanib reduced the decline in lung function by a similar magnitude in patients with IPF with baseline FVC >80% and <80% predicted.

Ciclosporin

A multicentre RCT[29] that evaluated the efficacy and safety of ciclosporin with low-dose corticosteroids compared with cyclophosphamide with low-dose corticosteroids for IPF treatment was identified. The primary endpoint was a change in FVC between baseline and 48 weeks. Ninety-nine patients were included in the study. The findings showed no significant difference between the ciclosporin and cyclophosphamide groups with regard to either adverse effects or the change in FVC between baseline and 48 weeks.

Carlumab

A phase II, randomised, double-blind placebo-controlled trial [30] that evaluated the safety and efficacy of carlumab in the treatment of IPF in 129 patients was identified. Patients were randomised to three carlumab treatment groups (1 mg.kg[-1], 5 mg.kg[-1], or 15 mg.kg[-1]) or placebo. The primary endpoint was the rate of percentage change in FVC. A greater decline observed in all active treatment groups in FVC compared with placebo. No effect on disease progression, infection rates or mortality was observed. SGRQ scores showed a nonsignificant trend toward worsening with active treatment. A higher proportion of patients with one or more serious adverse events was observed in the 5 mg.kg (-1) group (53.1%) compared with 1 mg.kg (-1) (15.2%), 15 mg.kg (-1) (21.9%) and placebo (46.4%), while no unexpected serious adverse events were noted. The authors concluded that it is unlikely that carlumab provides benefit to IPF patients.

Warfarin

A post hoc analysis of three RCTs [31] that had evaluated the effect of medically indicated anticoagulation on mortality and other clinical outcomes in IPF was identified. Patients (n=624) randomised to placebo from three controlled trials in IPF were analysed by oral anticoagulant use. End-points included all-cause and IPF-related mortality, disease progression, hospitalisation, and adverse events, over 1 year. Unadjusted analyses demonstrated significantly higher all-cause and IPF-related mortality at 1 year in baseline anticoagulant users versus nonusers (15.6% versus 6.3%, and 15.6% versus 3.9%, respectively). In multivariate analyses, baseline use of anticoagulants was an independent predictor of IPF-related mortality (hazard ratio 4.7), but not other end-points. Rates of bleeding and cardiac events did not differ significantly between groups. The authors concluded that use of anticoagulants for non-IPF indications may have unfavourable effects in IPF patients.

Combined treatments

A double-blind, modified placebo-controlled, randomised phase II trial [32] of pirfenidone in Chinese patients with IPF was identified. Chinese patients with IPF randomly assigned to receive either oral pirfenidone plus N-acetylcysteine (n=38) or placebo plus N-acetylcysteine (n=38) for 48 weeks. The primary endpoints were the changes in FVC and walking distance and the lowest blood oxygen level during the 6-minute walk test (6MWT) at week 48. At the 24th week, the mean decline in FVC and during the 6MWT in the pirfenidone group was significantly lower than that in the control group. However, there was no significant difference between the two groups at the 48th week. The pirfenidone treatment group did not achieve the maximal distance difference on the 6MWT at either the 24th or the 48th week. But pirfenidone treatment prolonged the progression-free survival time in the IPF patients. In the pirfenidone group, the adverse event rate (52.63%) was higher than that in the control group (26.3%). Rash was more common in the pirfenidone group. Compared with placebo combined with high-dose N-acetylcysteine, pirfenidone combined with high-dose N-acetylcysteine prolonged the progression-free survival of Chinese patients with mild to moderate impairment of pulmonary function.

A double blind phase II RCT [33] was identified that assessed the safety and tolerability of N-acetylcysteine and pirfenidone combination therapy in IPF. The study carried out at 48 sites in eight countries. Patients with IPF on pirfenidone (for 8 weeks or longer) were randomly assigned to receive oral N-acetylcysteine (n=60) or placebo (n=62) for 24 weeks. The primary endpoint was assessment of adverse events, which were collected at each visit and for 28 days after the last dose of study drug. The occurrence of at least one adverse event, adverse events related to study treatment, and the number of patients experiencing severe adverse events, life-threatening adverse events or death was similar between treatment groups. In the exploratory analysis, change in FVC indicated

that clinical benefit from addition of N-acetylcysteine to pirfenidone is unlikely, with the possibility of a harmful effect in patients with IPF. The authors concluded that the findings from the study suggest that addition of N-acetylcysteine to pirfenidone does not substantially alter the tolerability profile of pirfenidone, and is unlikely to be beneficial in IPF.

Comparison of different pharmacological treatments

A Health Technology Assessment review[34] was identified 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. Few interventions had any statistically significant effect on IPF and a lack of studies on palliative care approaches was identified. The model base-case results showed increased survival for 5 drug treatments compared with best supportive care. The authors concluded that general recommendations about cost-effectiveness could not be made owing to limitations in the evidence base.

Another network meta-analysis [35] was identified that evaluated pharmacological treatments for IPF and analysed their efficacy via Bayesian network meta-analysis and pairwise indirect treatment comparisons. 30 eligible studies that evaluated 16 unique treatments were included. Under both the fixed-effect and random-effect models for respiratory-specific mortality, no treatments performed better than placebo. For all-cause mortality, pirfenidone and nintedanib had effects with trend towards significance. Markedly, for respiratory-specific mortality, all-cause mortality, and decline in percent predicted FVC, nintedanib and pirfenidone were the same and no clear advantage was detected. The author concluded that although two treatments have been approved for IPF on the basis of reduced decline in pulmonary function, neither one has a clear advantage on mortality outcomes.

Third network meta-analysis [36] that investigated the effectiveness of treatments for IPF was identified. A total of 11 RCTs of pirfenidone, nintedanib or N-acetylcysteine were included. Only two treatments, pirfenidone and nintedanib produced a statistically significant slowing in the rate of FVC decline compared with placebo. In an indirect comparison, results indicated that nintedanib was statistically significantly better than pirfenidone in slowing FVC decline. Indirect comparisons showed no significant difference in rate of mortality between nintedanib and pirfenidone groups.

Forth Bayesian network meta-analysis [37] was identified that assessed the effects of different treatments for IPF on mortality and serious adverse events. A total of 19 RCTs (5,694 patients) comparing 10 different interventions with placebo and an average follow-up period of 1 year were included. Surface under the cumulative ranking curve analysis suggested nintedanib, pirfenidone, and sildenafil are the three treatments with the highest probability of reducing mortality in IPF. Indirect comparison showed no significant difference in mortality between pirfenidone and nintedanib and sildenafil or nintedanib and sildenafil. Sildenafil, pirfenidone, and nintedanib were ranked second, fourth, and sixth out of 10 for serious adverse events. The authors concluded that in the absence of direct comparisons between treatment interventions, this network meta-analysis suggests that treatment with nintedanib, pirfenidone, and sildenafil extends survival in patients with IPF. The serious adverse events of these agents were similar to the other interventions and were mostly related to dermatologic and gastrointestinal signs.

A systematic review [38] was identified that assessed the effectiveness and safety of the pirfenidone, nintedanib and N-acetylcysteine for IPF treatment. Ten studies (n=3,847 IPF patients) were included in this study. The results showed that both pirfenidone and nintedanib, but not N-acetylcysteine, were significantly effective in reducing FVC decline and the risk of FVC >10% decline in percent predicted over 12 months. Nintedanib significantly protected against the risk of acute exacerbation and mortality. Pirfenidone and nintedanib showed a similar and good safety profile, whereas N-acetylcysteine provided a signal for increased adverse events.

Topic expert feedback

Topic experts specified that since the guideline has been published, nintedanib and pirfenidone, the two important disease modifying drugs, have been reviewed and approved by NICE technology appraisals that should be integrated into guideline.

Impact statement

N-acetylcysteine

This evidence is unlikely to impact on recommendations in CG163.

The evidence from 2-year and 4-year surveillance reviews suggests that N-acetylcysteine had no beneficial effect on changes in FVC, changes in predicted carbon monoxide diffusing capacity, rates of adverse events, or death rates. However a significant effect in favour of N-acetylcysteine was found on decreases in percentage of predicted vital capacity and 6 minutes walking test distance.

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. 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 2-year surveillance review found 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 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.

The 2-year surveillance review also found 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. We did not find new evidence for this intervention at the 4-year surveillance review.

Sildenafil

This evidence is unlikely to affect recommendations in CG163.

The 2-year surveillance review found 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.

Evidence from 4 –year review based on indirect comparison suggests that sildenafil may extend survival in patients with IPF. The study reported no other benefits for treatment with sildenafil in IPF.

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 disturbances. The evidence is unlikely to impact on guidance because it derived from a post-hoc sub-analysis and indirect comparison.

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 the 2-year surveillance review. We did not find new evidence for this intervention at the 4-year surveillance review.

Pirfenidone

The new evidence is unlikely to have an impact on CG163.

A recommendation in CG163 refers readers to 'Pirfenidone for the treatment of IPF (NICE TA282), which recommends pirfenidone as a possible treatment for some people with IPF. TA282 is currently undergoing an update and the expected publication date is October 2016.

The evidence identified at 2-year and 4-year surveillance reviews indicates that that treatment with pirfenidone resulted in clinically meaningful reductions in disease progression and long-term treatment with pirfenidone is safe and generally well tolerated. The evidence from 4-year review is emphasising on wider use of the drug in patient with milder disease.

This information will be passed onto the TA team for consideration.

Nintedanib

This evidence is unlikely to impact on CG163. NICE technology appraisal on nintedanib published July 2016 recommends nintedanib as a possible treatment for some people with IPF. Nintedanib was not reviewed and considered in CG163. The recommendations need to acknowledge the technology appraisals TA379 on nintedanib for treatment of IPF.

Ciclosporin

Ciclosporin was not considered in CG163 for treatment of IPF. The new evidence showed that it is unlikely that ciclosporin provides benefit to patients with IPF therefore no impact on current recommendations is anticipated.

Carlumab

Carlumab was not considered in CG163 for treatment of IPF. The new evidence showed that it is unlikely that carlumab provides benefit to patients with IPF therefore no impact on current recommendations is anticipated.

Warfarin

This evidence is unlikely to impact on CG163. The new evidence suggests that use of anticoagulants for non-IPF indications may have unfavourable effects in IPF patients. This supports the current recommendation that indicates do not use warfarin for treatment of IPF.

Macitentan

This evidence is unlikely to impact on CG163. The 2-year surveillance review found 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. We did not find new evidence for this intervention at the 4-year surveillance review.

Combined treatments

New evidence on pirfenidone combined with N-acetylcysteine found that the treatment is unlikely to be beneficial in IPF. This combined treatment was not considered in CG163 and because there is no evidence of beneficial effects of the treatment identified, new evidence is unlikely to change current guideline recommendations.

Comparison of different pharmacological treatments

The new evidence is unlikely to impact on CG163.

Overall findings from 4 network meta-analyses on different pharmacological treatments for IPF showed that pirfenidone and nintedanib are the most effective drugs for treatment of IPF. The findings were evaluated on the basis of reduced decline in pulmonary function, mortality outcomes and safety profile.

Both pirfenidone and nintedanib are evaluated by NICE technology appraisal (NICE TA282 and NICE TA379 respectively).

Topic experts indicated that since the guideline has been published the two important disease modifying drugs (nintedanib and pirfenidone) have been reviewed and approved by NICE TA that should be integrated into guideline.

CG163 refers to NICE TA282 for IPF treatment with pirfenidone however nintedanib was not reviewed and considered in CG163. The recommendations need to acknowledge the technology appraisals TA379 on nintedanib for treatment of IPF. TA379 is in NICE pathway for CG163.

New evidence is unlikely to change guideline recommendations.

163 – 14 Which measures can be taken to minimise the occurrence/severity of adverse events when undergoing pharmacological treatment for IPF?

Recommendations derived from this question

The same recommendations were derived from this question as in 136-13.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Management – lung transplantation

163 – 15 What is the optimal timing to consider a patient with IPF for lung transplantation referral?

Recommendations derived from this question

1.5.16 Discuss lung transplantation as a treatment option for people with idiopathic pulmonary fibrosis who do not have absolute contraindications. Discussions should:

- take place between 3 and 6 months after diagnosis or sooner if clinically indicated
- be supported by an interstitial lung disease specialist nurse
- include the risks and benefits of lung transplantation
- involve the person's family and carers with the person's consent.
- (See recommendations 1.5.5 – 1.5.10 about best supportive care.)

1.5.17 Refer people with idiopathic pulmonary fibrosis for lung transplantation assessment if they wish to explore lung transplantation and if there are no absolute contraindications. Ask the transplant centre for an initial response within 4 weeks.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Management - ventilation

163 – 16 In acute or acute-on chronic respiratory failure in patients with IPF, what is the value of non-invasive and invasive ventilation?

Recommendations derived from this question

1.5.18 A respiratory physician or specialist nurse with an interest in interstitial lung disease should discuss the poor outcomes associated with mechanical ventilation (including non-invasive mechanical ventilation) for respiratory failure with people with idiopathic pulmonary fibrosis. These discussions should ideally take place between 3 to 6 months after diagnosis or sooner if clinically indicated. (See recommendations 1.5.5 – 1.5.10 about best supportive care.)

1.5.19 Do not routinely offer mechanical ventilation (including non-invasive mechanical ventilation) to people with idiopathic pulmonary fibrosis who develop life-threatening respiratory failure.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Review and follow-up

163 – 17 How often should a patient with confirmed diagnosis of IPF be reviewed?

Recommendations derived from this question

1.6.1 In follow-up appointments for people with idiopathic pulmonary fibrosis:

- assess lung function
- assess for oxygen therapy
- assess for pulmonary rehabilitation
- offer smoking cessation advice, in line with Smoking cessation services (NICE public health guidance 10)
- identify exacerbations and previous respiratory hospital admissions
- consider referral for assessment for lung transplantation in people who do not have absolute contraindications (see recommendations 1.5.16 and 1.5.17)
- consider psychosocial needs and referral to relevant services as appropriate
- consider referral to palliative care services
- assess for comorbidities (which may include anxiety, bronchiectasis, depression, diabetes, dyspepsia, ischaemic heart disease, lung cancer and pulmonary hypertension).

1.6.2 Consider follow-up of people with idiopathic pulmonary fibrosis:

- every 3 months or sooner if they are showing rapid disease progression or rapid deterioration of symptoms **or**
- every 6 months or sooner if they have steadily progressing disease **or**
- initially every 6 months if they have stable disease and then annually if they have stable disease after 1 year.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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163 – 18 In which healthcare setting and by whom should a review appointment for patients with confirmed IPF be conducted

Recommendations derived from this question

The same recommendations were derived from this question as in CG136-17.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE's research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision will be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.

  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 What is the value of bronchoalveolar lavage in people in whom idiopathic pulmonary fibrosis is considered the most likely diagnosis when clinical and CT findings are insufficient to support a confident diagnosis?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

RR – 02 What is the value of surgical lung biopsy in people in whom idiopathic pulmonary fibrosis is considered the most likely diagnosis when clinical and CT findings are insufficient to support a confident diagnosis?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

RR – 03 Does pulmonary rehabilitation improve outcomes for people with idiopathic pulmonary fibrosis?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.

Surveillance decision

The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.

RR – 04 Does ambulatory oxygen improve outcomes in idiopathic pulmonary fibrosis?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.

Surveillance decision

The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.

RR – 05 Is anti-reflux therapy an effective treatment for idiopathic pulmonary fibrosis?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation should be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.

Other research recommendations

The following research recommendations were not deemed as priority areas for research by the guideline committee. No decisions will be taken the status of these research recommendations.

What is the value of transthoracic echocardiography in detecting pulmonary hypertension and 20 determining prognosis in people with idiopathic pulmonary fibrosis?

No new information was identified at any surveillance review.

What is the agreement between radiologists in the interpretation of CT in patients with suspected 19 idiopathic pulmonary fibrosis?

No new information was identified at any surveillance review.

RR – 08 What is the feasibility of a formal 'CT scoring system' to assess disease severity in patients with 15 suspected idiopathic pulmonary fibrosis?

No new information was identified at any surveillance review.

RR – 09 What is the utility of a formal CT scoring system in determining outcome in patients with suspected 8 idiopathic pulmonary fibrosis?

No new information was identified at any surveillance review.

RR – 10 Does nocturnal oxygen improve outcomes in idiopathic pulmonary fibrosis?

No new information was identified at any surveillance review.

RR – 11 Does short-burst oxygen therapy improve outcomes in idiopathic pulmonary fibrosis?

No new information was identified at any surveillance review.

RR – 12 Is corticosteroid therapy an effective treatment for IPF?

No new information was identified at any surveillance review.

RR – 12 Is co-trimoxazole an effective treatment for IPF?

No new information was identified at any surveillance review.

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