National Institute for Health and Clinical Excellence

Idiopathic pulmonary fibrosis
Guideline Consultation Comments Table
11 January 2013 – 22 February 2013

Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
Association of Respiratory Nurse Specialists	1	Full	9	review and follow up section	Should include an ECHO for increasing breathlessness to eliminate PHT (pulmonary hypertension)	Thank you. We have amended the wording of recommendation 1.6.1, so that the last bullet point of this recommendation now covers assessment for comorbidities.
Association of Respiratory Nurse Specialists	2	Full	10	17	Blood tests for precipitins and antibodies should be inserted as these are essential in patients with yet undeclared connective tissue disease associated ILD.	Thank you. We have amended the wording of recommendation 1.2.1 for greater clarification.
Association of Respiratory Nurse Specialists	3	Full	15	Section 1.6.3	Relaxation via an OT is useful and psychology referral for diagnosis acceptance is often useful for the patients.	Thank you. The GDG agree with the point raised and added this additional information to the 'linking evidence to recommendation' section, which discusses the rationale behind the relevant recommendations. Please see section 8.6 of the full guideline.
Association of Respiratory Nurse Specialists	4	Full	18	Section 1.8.2	Nocturnal oxygen should be regularly assessed for signs for developing PHT and also nocturnal sleep hypoxia	Thank you. The GDG agree with your comment and have highlighted the importance of assessing nocturnal oxygen in a research recommendation, as no evidence for nocturnal oxygen in people with IPF was

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						found. Please see research recommendation P8 in appendix P.
Boehringer Ingelheim	6	Appendix	345	18	The model assumes that respiratory hospitalisation influences mortality rates but does not allow for an impact upon quality of life (QoL). Increased mortality would naturally lead to a decrease in QoL. Also, hospital-associated exacerbations in COPD or asthma may lead to reductions in QoL; therefore the decrement for patients with IPF who experience hospitalisation might be expected to be even more severe."	Thank you for your comment. There was no evidence to inform the effect of hospitalisation on QoL in the IPF population. As rate of hospitalisation was the same in the rehabilitation and no rehabilitation strategies (again due to no evidence to inform this relationship) this simplification regarding quality of life would not impact on the results of the incremental analysis presented. We acknowledge that further research is required to inform future analyses.
Boehringer Ingelheim	7	Appendix	345	30	The model assumes that respiratory hospitalisation influences mortality rates but does not allow for an impact upon FVC % predicted.	Thank you. We have amended the appendix for greater clarification. We now note this is due to a lack of data. However, in line with evidence retrieved for the prognostic review, hospitalisation does influence probability of mortality and this has been captured in the model accordingly.
Boehringer	8	Append	346	1	The model structure prohibits 'backward' improvements	Thank you. The developers

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Ingelheim		ix			(i.e. improvement in a patients' FVC% predicted over a 1 month cycle). This is unsupported by the evidence published by Swigris (2010) and "UK data source" shown on pg. 352; table 127 which suggest that over 12% improvements in FVC% predicted can be achieved in some patients (6% Swigris (2010)). The justification for this can be found on appendix page 345 line 31.	revisited the justification in light of your comment and acknowledge this is an assumption made within the model, in absence of data to estimate mortality for this group of patients. We now acknowledge this and highlight a sensitivity analysis was conducted alongside the justification in section L.2.2.1 . Reference is made to section L.2.2.3 for details of the analysis.The analysis showed that results remained robust to increasing and decreasing the risk of mortality in the proportion of patients who may experience an increase in FVC% predicted value.
Boehringer Ingelheim	1	Full	29	46	Given the potential influence of this document, from the information provided there was not a 2nd reviewer to corroborate decisions during the inclusion/exclusion rounds of the literature review. Given that independent assessment by more than one researcher has been shown to markedly increase the reliability of the decision process (Centre for Reviews and Dissemination, 2008), the search did not minimize the potential for errors of judgement. Centre for Reviews and Dissemination (2008), Systematic Reviews: CRD's guidance for undertaking reviews in health care. Accessed at	Thank you. To minimise errors and any potential bias in the assessment, two reviewers independently assess a random selection of studies. Any differences arising from this were then discussed with the GDG. Further detail on this process has now been added to section 3.3.1 in the methodology chapter of the full guideline.

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					http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf on 7th Feb 2013.	
Boehringer Ingelheim	2	Full	43	14	Further research considerations may include: 1) The need to develop or further validate a disease-specific quality of life tool. 2) The investigation of IPF exacerbations, how they are defined. 3) The investigation into the impact exacerbations have on the course of the natural history of the disease. 3) Formalising the definition of grades of severity in IPF/ILD and how these grades impact on prognosis and response to treatment.	Thank you. The GDG had lengthy discussions to identify areas where further research was required when limited evidence was retrieved. The GDG considered evidence from SF-36 and St George's Respiratory Questionnaire for a number of clinical areas and also recognised that IPF-specific QoL tools have very recently been developed and validated, so did not feel that further research in this area would benefit from a research recommendation over those prioritised in the guideline. The GDG acknowledged that there is a lack of evidence investigating IPF exacerbations, but did not feel that further research in this area would benefit from a research recommendation over those prioritised in the guideline. The GDG have defined this term in the full guideline's glossary.

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						The GDG have provided guidance on assessing prognosis and did not feel that further research in this area would benefit from a research recommendation over those prioritised in the guideline. The research recommendations and criteria used for prioritisation can be found in appendix P.
Boehringer Ingelheim	3	Full	244	8	Warfarin costs – calculation requires review: Cost of drug = £12; Additional costs = £202 Total = £214 (not £204 which is stated)	Thank you. All drug costs and associated calculations have been revised to incorporate the latest unit costs during guideline development. The revised calculation is based on a unit cost of £0.78 per 3mg 28-tab pack (The Drug Tariff, March 2013). This now reads: Cost of drug = £10 Additional costs = £202 Total = £212 The update of unit costs did not affect the recommendations formulated.
Boehringer Ingelheim	4	Full	246	3	Section heading states "*Warfarin vs. Prednisolone"* but evidence statements are based on "*Warfarin + Prednisolone vs. Prednisolone" (pg.210)* comparison.	Thank you for your comment. The section heading and evidence statements have

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					Heading and statements would benefit from amendment.	been amended to read "*Warfarin + Prednisolone vs. Prednisolone"*
Boehringer Ingelheim	9	Full	246	30	Evidence statements used express the supporting data poorly e.g. *"Moderate quality evidence showed that sildenafil may be clinically more effective than placebo at reducing mortality but the direction of the estimate of effect could favour either intervention" (page 247 line 14).* A more appropriate and clear wording would be "*the data was inconclusive as to whether sildenafil was clinically more effective than placebo at reducing mortality".*	Thank you for your comment. Please note that evidence statements have been worded according to a standard format based on NICE methods. Please see the NICE guidelines manual for further information. National Institute for Health and Care Excellence. The guidelines manual 2012. Available from: **http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2012.jsp**
Boehringer Ingelheim	10	Full	250	3	Evidence statements incorrectly interpret the data on which they are based. "Low quality evidence showed that a combination of prednisolone + azathioprine is less effective than prednisolone alone at reducing mortality"; this though is unsupported by the evidence on which it is based which shows no statistical significance between treatment effects: Pg. 232 - Mortality: Summary of findings; effect; RR (95% CI) - 0.93 (0.29 to 2.97) Absolute, mean difference (95% CI) – 22 fewer per 1000 (from 218 fewer to 606 more). We would therefore suggest amending this statement to more accurately reflect the data.	Thank you for your comment. No minimal important difference was applied to the mortality outcome as the GDG considered that any decrease in mortality was a clinically important effect in IPF. Please see section 4.3.9 of the full guideline. We therefore interpreted a relative risk of 0.93 to show a small effect in favour of prednisolone alone.

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Boehringer Ingelheim	5	Full	292	5	The patient pathway is structured around Specialist care centres Nationally. It is important to the patient that they understand the benefits of being seen by the multi-disciplinary team in a specialist centre to effectively manage a rare disease. Good patient experience has already been identified in the NICE clinical guideline 138, however any specific patient guidance for IPF should make this recommendation clear for a Specialist centre care.	Thank you. The GDG considered that the points raised are sufficiently covered in recommendations: 1.2.2, 1.2.3, 1.3.1 and 1.3.3.
British Infection Association	1	Full	General		Please can you substitute the word "histopathologist" for "pathologist" throughout this document? The term "pathologist" includes Microbiologists, Biochemists, Haematologists and so on as reflected for example in the membership of the Royal College of Pathologists. You really mean "histopathologist" in the context of your document.	Thank you for your comment. The word 'pathologist' has been changed to, 'histopathologist' throughout the document.
British Lung Foundation	1	NICE	General		The British Lung Foundation (BLF) welcomes the draft guideline for Idiopathic Pulmonary Fibrosis (IPF), for which there is a pressing need. We are generally very happy with the content of the draft guideline – and its role both in analysing and collating evidence for clinical approaches and in delivering practical recommendations on patient management, information and support. The comments below relate to the NICE version only, as we regard the top-line recommendations as being critical to effective implementation of the guideline.	Thank you for your comment.
British Lung Foundation	2	NICE	13	1.3.1	**Recommendation 1.3.1.** We welcome the recommendation for accurate and clear information (verbal and written) to people with IPF, their families and carers throughout the pathway. However, the guideline should state explicitly that this should include information on wider	Thank you for your comment. The GDG considered the points raised are already sufficiently covered within recommendation 1.3.1, but

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					welfare and lifestyle issues, as well as purely 'medical' information. IPF necessitates sudden and considerable changes in the lifestyles and financial situations of patients, their families and carers. It is important that health care professionals are able either to provide or to signpost information on issues such as welfare benefits, social care, lifestyle adaptations and support for carers – but our experience suggests that this is less likely to be provided than medical information. The BLF offers a range of written information on welfare and lifestyle issues, as well as a helpline which patients, families and carers can call for specialist advice.	have added additional information on the provision of welfare and lifestyle issues to the 'linking evidence to recommendation' section, which discusses the rationale behind the relevant recommendations. Please see sections 6.5 and 7.11 of the full guideline. Please also see the IFP (information for the public
British Lung Foundation	3	NICE	14	1.4.2	**Recommendation 1.4.2**. We welcome the recognition in this recommendation that a combination of sensitivity and clarity is required in discussing prognosis with newly diagnosed patients. However, we believe that there should be an additional recommendation encouraging referrals to professional counselling services and other sources of emotional support if required. Coming to terms with IPF diagnosis and prognosis can be an extremely distressing experience, especially as diagnosis may be greeted first with confusion and in some cases even relief (e.g. that it is not lung cancer), before the full meaning of the prognosis becomes apparent. The evidence considered in the full guideline supports the inclusion of counselling and emotional support within the recommendations. The evidence statements for the section on psychosocial care (section 9.5) note a need among patients for 'comprehensive family support/counselling programs', and a 'lack of referrals' for	Thank you. We have amended the wording of recommendations 1.5.7 and 1.6.1, for greater clarification.

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					behavioural counselling. Inclusion of a specific recommendation for referrals to counselling and emotional support if appropriate would help to address this need.	
British Lung Foundation	4	NICE	15	1.6.1	**Recommendation 1.6.1.** Best supportive care also should include referral to counselling or emotional support services if required, for the reasons outlined in the comment on R1.4.2 above.	Thank you. We have amended the wording of recommendations 1.5.7 and 1.6.1 for greater clarification.
British Lung Foundation	5	NICE	16 -18	1.7	**Recommendation 1.7.** We note the lack of conclusive evidence to support the use of drugs to increase the survival of people with IPF. However, we believe that the guideline should include a specific recommendation for clinicians to discuss participation in clinical trials with IPF patients where appropriate. In the BLF's experience, IPF patients often welcome participation in clinical trials, which can represent the only opportunity for pharmacological treatment, as well as providing an opportunity to assist with the development of future treatments. There is a pressing need for research into pharmacological treatments for IPF, and the BLF would like to see more research into new therapies to tackle the underlying processes of IPF. At present, researchers may struggle to find patients to take part in clinical trials, especially if they require patients with a diagnosis confirmed by biopsy. The recommendation should include the need for a full and honest discussion with the patient about the implications and any possible risks of taking part in a clinical trial. It should also highlight the need to ensure that patients who participate in clinical trials receive adequate information and emotional support. It is important to recognise that the initial hope and optimism that participation in a trial can	Thank you for your comment. Recommending the participation in clinical trials is beyond the remit of NICE guidelines, but the GDG acknowledge that it is of important value to progress knowledge in this disease.

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					bring may give way to great disappointment if the treatment does not have a positive effect.	
British Thoracic Society	1	Full	General		The document does not include reference to immunological testing in the diagnostic pathway. This area is difficult, but no statement on its use will send out the message that it should not be performed. IPF is diagnosed as a UIP pattern (on CT mostly) excluding all other causes of UIP, and immunological testing is part of this.	Thank you. We have amended the wording of recommendation 1.2.1 to include performing blood tests, for greater clarification.
British Thoracic Society	3	Full	40	21 and 25	In the section on the use of oxygen, the recommendation is worded as if the use of oxygen is for the treatment of breathlessness alone. The BTS Guideline on emergency oxygen use in adult patients outlines oxygen use as a treatment for hypoxaemia and flow rates determined using target saturations, both in the acute and home settings. The reference in the IPF guidelines may cause confusion. It is not clear from the summary of evidence whether the studies demonstrating the effects of oxygen were used in those with or without hypoxaemia, or a combination, and what effect it had on the oxygen saturation as well as the breathlessness, and this needs clarification. The assumption is that the patients were given oxygen because they had breathlessness due to hyoxaemia, which is the likely situation, but the evidence should make this clear and the recommendation requires clarity.	Thank you. The GDG agree with the point you have raised and added this in to the 'linking evidence to recommendation', section, which discuss the rationale behind the relevant recommendations. Please see section 8.6 of the full guideline. The evidence for this review has been presented as reported in the studies and therefore, data for patients with hypoxemia has been presented if it has been reported in the study. The GDG agree that the concerns you raise are limitations of the studies and the developers have downgraded the evidence accordingly.
British Thoracic	2	Full	40	32	Studies have consistently demonstrated associations	Thank you for your comment.

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Society			41 179 -181 252-265	-34 35-37	between gastro-oesophageal reflux and IPF. There have been no RCTs looking at anti-reflux treatment, but a recommendation to treat associated reflux seems reasonable given that it is relatively safe and cheap. However, we need to be clear that anti-reflux treatment does not equate to acid suppression with PPIs. Many patients with reflux do not report oesophageal symptoms such as dyspepsia. PPIs do not treat reflux, they just suppress gastric acid production. Gastric refluxate contains many other agents potentially toxic to the lung, e.g. enzymes, bile salts, etc. Better anti-reflux treatment might comprise motility agents (e.g. metoclopramide, domperidone, azithromycin) or surgery (e.g, Nissen fundoplication or roux-en-Y gastric bypass). A note should be included to this effect. Repeated references to the NICE dyspepsia guideline (CG 17) are misleading and should be removed.	The GDG have acknowledged the points you raise, but due to the lack of evidence for PPIs in people with IPF, the GDG agreed that reflux symptoms should be treated in line with NICE guideline CG17, which provides guidance on treating GORD with PPIs. The potential role of treating reflux as a treatment for IPF is currently an area for further research as outlined in research recommendation P12 in appendix P. The other anti-reflux treatments mentioned are outside the remit for this guidance
Department of Health	1	Full	General		The Department of Health has no substantive comments to make, regarding this consultation	Thank you for your comment.
InterMune	1	FULL	26	21	The GDG have defined MID's for various outcomes. However, given the lack of data that exists, this could be potentially misleading as these are cohort MID's. They may be suitable for assessing interventions in clinical trials, but are less useful for assessing individual patients.	Thank you. The GDG acknowledge the point you raise, but have not used the thresholds for assessing individual patients. The GDG have also not made recommendations solely on the basis of MIDs either, because of the need to take into account cost effectiveness, but

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						the MIDs assisted the GDG to assess whether one treatment is more clinically effective than another, or more effective than no treatment.
InterMune	2	FULL	34	11	As assessment will most likely occur in primary care, how will knowledge of this very important step be passed on to GP's?	Thank you for your comment. The GDG were very aware of this issue and have acknowledged this in recommendation 1.1.1. Increasing awareness in primary care will also be specifically targeted during the implementation of this guideline.
InterMune	3	FULL	36	8	How is an assessment of ineffective therapies made in a condition that will worsen? How can we ensure we won't precipitate worsening health?	Thank you for your comment. There was the recognition that patients can demonstrate serious adverse events profiles with the pharmacological interventions and may require withdrawal of ineffective therapies and thus may need the expertise of the ILD team to tailor alternative regimens for patients through the delivery of continued care. The GDG also considered that regular review provided the opportunity to discontinue ineffective or cost ineffective management.

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InterMune	4	FULL	36	13	There should be clear mention here that a licensed medication for mild to moderate IPF exists (pirfenidone). Regardless of the outcome of the NICE TA for pirfenidone, this information should not be suppressed or relegated to a footnote.	Thank you for your comment. We have now added the following standard wording to the pharmacological section: *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 TA 282).*
InterMune	5	FULL	37	1	Specialist Centre follow-up should be mandatory for all patients at least once per year. Local follow-up should be every 3 months to monitor disease progression and for early specialist intervention and access to services (e.g. End of Life, counselling etc.). We suggest that this could be achieved in an innovative way such as utilising homecare or telehealth to reduce cost.	Thank you for your comment. The GDG considered that follow-up to monitor disease progression in people with IPF was sufficiently covered in recommendations 1.4.1 and 1.6.2. The GDG did not consider that the guideline should specify what mode of delivery or location of follow-up appointments should take.
InterMune	6	FULL	41	15	While the Clinical Guideline should clearly include proper consideration of pirfenidone, we suggest that in this specific section of the Draft, the text should be amended to include, at a minimum, the following wording (in bold): ***"Pharmacological interventions 15*** ***There is no conclusive evidence to support the use of any drugs to increase the survival of people with idiopathic pulmonary fibrosis.***	Thank you for your comment. We have now added the following standard wording to the pharmacological section: *For guidance on pirfenidone for the management of idiopathic pulmonary fibrosis, refer to Pirfenidone for the treatment of idiopathic*

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					Advise the person with idiopathic pulmonary fibrosis ***that pirfenidone is a licensed drug for treating patients with mild-to-moderate idiopathic pulmonary fibrosis****. If a patient has an unmet medical need (e.g., is contraindicated to pirfenidone), patients should be informed that oral N-acetylcysteine is used for managing idiopathic pulmonary fibrosis,* ***but that it has not been reviewed by a regulatory agency for safety and effectiveness in IPF. As such,*** *its benefits are uncertain."* (Emphasis added).	*pulmonary fibrosis (NICE technology appraisal guidance TA 282).* *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 medicines – guidance for doctors for further information.*
InterMune	7	FULL	41	16	While InterMune believes that the current technology appraisal of pirfenidone will result in a positive recommendation for use in NHS patients (and will presumably be added to the Clinical Guideline at that stage), irrespective of the outcome of the appraisal, consideration of pirfenidone may not reasonably be excluded from the Clinical Guideline.	Thank you for your comment. We have now added the following standard wording to the pharmacological section: *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 TA 282).*
InterMune	8	Full	41	38	[Related to footnote] - Moreover, the informed consent	Thank you for your comment.

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					section of the footnote should be expanded to ensure patients receive adequate consent before receiving an unlicensed medicine. This specifically requires patients to be told that a licensed alternative exists in the UK and the reasons why the patient is not being treated with the drug. Patients should therefore be informed of the following elements: • **that pirfenidone, a safe and effective drug for treating IPF, has been approved by the European Commission following a review by the European Medicines Agency;** • **the drug is authorized for use in the UK;** • **that the proposed treatment -- oral N-acetylcysteine -- is not licensed for IPF and therefore the effectiveness and safety of the product is uncertain as it has not been reviewed by a regulatory authority; and** • **include an explanation of the rationale for proposing use of an unlicensed/off-label drug (i.e., e.g., contraindication or reduced cost as the case may be).**	Standard wording has now been applied to the IPF NICE version and full guideline: *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 TA 282).* *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 medicines – guidance for doctors for further information*. The recommendation is not proposing the use of oral NAC, but advising the specialist clinician to discuss all treatment options with the

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						person with IPF. The GDG acknowledged that oral NAC is unlicensed for the treatment of IPF in the UK and that informed consent would need to be obtained before it is prescribed on a patient named basis. This is captured in the linking evidence to recommendation sections of the full guideline. Please see section 11.6.
InterMune	9	FULL	43	4	What proportion of elderly males with IPF are misdiagnosed with COPD or other lung conditions?	Thank your comment. This query is beyond the scope of this guideline.
InterMune	10	FULL	43	4	Do specialist centres improve outcomes for patients with IPF?	Thank you for your comment. The GDG agreed that a multidisciplinary team will provide a confident diagnosis of IPF as indicated in recommendations 1.2.2 and 1.2.3. The GDG believe that achieving a more confident diagnosis with ultimately help clinicians identify a clearer management plan and may improve psychosocial outcomes and QoL for some, compared to patients not having a firm diagnosis. Please refer to the 'linking evidence to recommendations' section in

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						section 5.5 of the full guideline.
InterMune	11	FULL	197	33	The GDG should also review pirfenidone to the same level of scrutiny as the other interventions as it is unfair and unbalanced that recommendations for some medications (e.g. NAC which is unlicensed) are made with a lower level of scrutiny whereas pirfenidone (which is licensed) shall only appear if the NICE TA approves it.	Thank you for your comment. The scope for this guideline does not include pirfenidone due to the development of the pirfenidone TA 282, so the GDG have agreed to cross-refer to the pirfenidone TA 282 as appropriate. Standard wording has now been applied to the IPF NICE version and full guideline: *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 TA 282).* The recommendation is not proposing the use of oral NAC, but advising the specialist clinician to discuss all treatment options with the person with IPF. Standard wording has now been applied to the IPF NICE version and full guideline: *At the time of publication (June 2013), N-acetylcysteine did not*

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						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 medicines – guidance for doctors for further information.
InterMune	12	NICE	3	13	Currently, the document confirms the median survival time for an IPF patient is "approximately 3 years from the time of diagnosis". Therefore it is critical to ensure early diagnosis as prognosis is difficult to estimate at all stages and may only become apparent after a sustained period of specialist follow-up.	Thank you for your comment.
InterMune	13	NICE	6	4	This clear and concise description of clinical features to aid in early diagnosis is welcomed. How these are incorporated into the pending ILD service specification and then communicated to CCG and other medical staff is imperative for success.	Thank you for your comment.
InterMune	14	NICE	7	2	The minimum composition of the MDT for diagnosis of IPF is valued. Some specialist centres currently treating patients may not have access to all of these resources; therefore what plans are in place to reduce any potential impact on patient services in the future?	Thank you. We acknowledge your point. However, it was beyond the scope of the guideline to comment on the optimal implementation and commissioning practice to implement the recommendation. A variety of

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						tools to assist implementation will be available online alongside the guideline.
InterMune	15	NICE	14	14	It states here "Do not use the 6-minute walk distance at diagnosis to estimate prognosis" but then in the next statement 1.5.1 it is claimed that patients should be assessed for pulmonary rehabilitation with a possibility of the 6-minute walk test "at the time of diagnosis". This apparent contradiction in guidance needs further clarification in light of 6MWD and FVC being considered as independent predictors of mortality.	The GDG considers that 6MW distance should not be used as a measure to indicate prognosis, as it does not add further prognostic information to that obtained by measuring FVC% predicted at baseline. It could therefore not be recommended for this purpose. However, the GDG acknowledges the 6 minute walk test may be used for a variety of purposes, such as when assessing whether pulmonary rehabilitation is appropriate for people with IPF. It was felt that further comment regarding the test could not be made as the evidence for its use in this respect had not been reviewed. Further detail is available in chapters 6 and 7 of the full guideline.
InterMune	16	NICE	14	23	The reassessment schedule at 6-month or 12-month intervals may be considered too long in the context of the 3 year median survival. Specialist Centre follow-up should be mandatory for all patients at least once per year. Local	Thank you for your comment. Consideration was given to the life expectancy and probability of a change in clinical need

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					follow-up should be every 3 months to monitor disease progression and for early specialist intervention and access to services (e.g. End of Life, counselling etc.). We suggest that this could be achieved in an innovative way such as utilising homecare or telehealth to reduce cost.	when making recommendations associated with assessment and monitoring. There was no economic or clinical evidence to support a more frequent assessment than that recommended. The evidence regarding the most appropriate setting was not identified as part of the scope for this guideline and the GDG considers that local services should decide where appropriate follow-up should take place.
InterMune	17	NICE	15	24	Section 1.6.4 states "Assess the oxygen needs of people who have been hospitalised with IPF before they are discharged". We suggest that cost savings and QOL improvements could be achieved by innovative home care arrangements set up locally like those already included in QIPP COPD home oxygen pathway case studies.	Thank you for your comment. The design of innovative home care arrangements is beyond the scope of the guideline.
InterMune	18	NICE	16	17	There should be clear mention here that a licensed medication for mild to moderate IPF exists (pirfenidone). Regardless of the outcome of the NICE TA for pirfenidone, this information should not be suppressed or relegated to a footnote.	Thank you for your comment. We have now added the following standard wording to the pharmacological section: For guidance on the use of pirfenidone in people with IPF, see pirfenidone for the treatment of IPF (NICE TA 282).
InterMune	19	NICE	18	18	In section 1.8 - Review and follow-up - it is again	Thank you for your comment.

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					recommended that follow-up of patients with steadily progressing disease or every 6 months if they have stable disease and then annually". Specialist Centre follow-up should be mandatory for all patients at least once per year. Local follow-up should be every 3 months to monitor disease progression and for early specialist intervention and access to services (e.g. End of Life, counselling etc.). We suggest that this could be achieved in an innovative way such as utilising homecare or telehealth to reduce cost.	There was no economic or clinical evidence to support a more frequent assessment than that recommended. The evidence regarding the most appropriate setting was not identified as part of the scope for this guideline and the GDG considers that local services should decide where appropriate follow-up should take place.
Medicines and Healthcare products Regulatory Agency (MHRA)	1	Full	General		We ask you to ensure that the guideline uses the wording that was agreed between MHRA and NICE in June 2012 about off-label and unlicensed use of medicines for use in clinical guidelines.	Thank you. We can clarify that standard wording as agreed between NICE and the MHRA has been used throughout the guideline. *"At the time of publication ([month year]), [name of drug] 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 medicines – guidance for doctors for further information."*
Primary Care	1	Full	11		Terminology and definition	Thank you for your comment.

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Respiratory Society					There is confusion about the terminology in General Practice, which is briefly mentioned in the Introduction. The terms fibrosing alveolitis, cryptogenic fiibrosing alveolitis and diffuse parenchymal lung disease have all been used synonymously with pulmonary fibrosis or idiopathic pulmonary fibrosis. In one member Practice this confusion led to successful legal proceedings against the Practice. It is important that NICE , once and for all , should recommend a terminology which obviates this confusion. This should not be just merely be mentioned in an introductory paragraph, but as a key recommendation.	We have now defined the following terms in the full guideline's glossary and expanded the introduction to define the terms cryptogenic fibrosing alveolitis, idiopathic pulmonary fibrosis and non-specific interstitial pneumonia.
Primary Care Respiratory Society	2	NICE	General		Terminology is not mentioned at all in the NICE guideline which is a significant omission. See comments on terminology on Full guideline.	Thank you for your comment. We have now defined the following terms in the full guideline's glossary and expanded the introduction to define the terms cryptogenic fibrosing alveolitis, idiopathic pulmonary fibrosis and non-specific interstitial pneumonia.
Primary Care Respiratory Society	3	NICE	6		The pages containing the key recommendations appear to be duplicated – so section 'Key priorities for implementation' (p6) seems not very different from section 1 on p 10 Recommendations.	Thank you for your comment. It is part of NICE process to identify key priority recommendations for implementation. The full list of recommendations is then presented throughout the rest of the NICE guideline.
Pulmonary Fibrosis Wales	1	Full	General		We have had a look at the draft (which) we felt was very fair and informative. The draft had gone into great detail,	Thank you for your comment.

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					was clearly explained and covered all elements.	
Royal Brompton Hospital	1	Full	General		I support very strongly comments submitted by the Royal Marsden Hospital palliative care team regarding the need for formal palliative care involvement in advanced IPF, with regard to symptom control, advance care planning and rationalisation of resources. My involvement with the palliative care team has convinced me that although very motivated to try, I and my medical and nursing colleagues are not equipped with the skills to provide what is needed in this sphere. Nurse specialist involvement, although desirable, is likely to be available only in regional centres and at the very least, a period of training and mentoring would be needed. The document does, indeed, specify that access to specialist palliative care services is desirable but states also that symptomatic care can be largely provided by the respiratory physician. The model used here may be a terminal care model but formal palliative care consultative input to define the best use of palliative care expertise would be highly desirable.	Thank you for your comment. The GDG agree that it is a priority to ensure that patients have access to the full range of services offered by palliative care teams and consider that the level of palliative care input is adequately covered in recommendation 1.5.10. The full range of services would mean that symptomatic care would be provided by the palliative care team and not only by the respiratory physician.
Royal Brompton Hospital	2	Full	General		Much of the document is impressive but the prognostic section was done with a substandard review of the literature. I have not indicated page numbers because this applies to the whole prognostic section. Regarding serial PFT change, the three keynote series have been excluded (the three most heavily cited papers in Am J Respiratory Crit Care Med in 2003). Please refer to reference 125 ("Wells AU. Forced vital capacity as a primary end point in idiopathic pulmonary fibrosis treatment trials: making a silk purse from a sow's ear. Thorax. 2012"). This lists a number of studies omitted from the document. The baseline PFT prognostic evaluation is also very	Thank you for your comment. We are sorry that you feel that the prognostic evidence review was conducted with a substandard review of the literature. The GDG identified and agreed on specific criteria on which our intervention searches and inclusion/ exclusion criteria were set. The protocols for this prognostic evidence review can be found in appendix C.

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					skeletal. In virtually all of the serial PFT change studies, including a number omitted from the review, separate baseline PFT versus survival statements have been made. This has also been the case with some CT studies. Regarding CT scores versus mortality in IPF, the review has omitted the study of Kazerooni E and the whole corpus of studies from the Royal Brompton Hospital. The CPI study (Wells AU) was a prospective study and showed that disease extent scored on HRCT was strikingly predictive of mortality. The study of Antoniou KM et al showed exactly the same. All three of these studies were published in Am J Respir Crit Care Med. Although I would like to have been more helpful, the literature review for this whole section is so incomplete that I cannot be confident of supplying all missing references. I would urge you to start again and to explore all prognostic statements made in IPF. Titles of papers often refer to a single variable of interest but contain very substantial PFT and/or HRCT data which are not captured by searching explicitly for "PFT prognosis". At present, the prognostic section would be an embarrassment if published in its present form. This contrasts strikingly with the splendid job done elsewhere.	The studies you mention have all been checked against the relevant protocols and the GDG are confident with the reasons for exclusion. All the studies noted were identified by our search terms, however studies were not retrieved if they were not IPF specific or if they did not state the interventions specified in the review protocols for the guideline. Please see the methodology section 4.3.1 of the full guideline. Please see below (at the end of the table) for the list of studies you mention and their exclusion details. A full list of all full paper studies ordered for consideration in the full guideline against the guideline review protocols and their exclusion reasons can be found in found in appendix R.
Royal Brompton Hospital	1	NICE	17	8	I have misgivings that there is a quasi-recommendation that in IPF patients stable on established triple therapy, prednisolone and azathioprine should be withdrawn	Thank you for your comment. We have amended the wording of recommendation

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					("consider withdrawal"). I can assure the group that in the absence of hard data, there is a ground-swell internationally favouring continuation of triple therapy in IPF patients doing very well with this treatment. This view has been informally expressed by several members of the PANTHER authorship. The PANTHER data relate to very early toxicity, co-segregating strikingly with high dose steroid therapy in the first four months in a frail elderly population. I think you are taking a real risk "recommending" withdrawal of a treatment in individuals with unusually stable disease. I would not rule out the possibility that in the next year or two, a published statement might be made about a sub-group of IPF patients progressing rapidly/fatally following withdrawal of triple therapy. This is surely a situation in which it is possible to be neutral – instead of "considering withdrawal" (which pretty much states that withdrawal is desirable), it is surely better to acknowledge uncertainty regarding a scenario not examined in PANTHER and not take an obsequious view of the PANTHER findings. This commentator was amazed that, despite major early toxicity, there was no difference in PFT change between the PANTHER treatment groups, supporting the concept of IPF sub-groups doing better and worse with immunomodulation. The paper of Karloon, in press in Am J Respir Crit Care Med (and so not citable for another few weeks) is highly relevant Please consider whether you really need to take a stance on continuation of triple therapy in patients well established on the treatment and doing very well. This	1.5.13 for greater clarification.

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					scenario, I stress again, is NOT evaluated in PANTHER. Why go out on a limb?	
Royal College of Nursing	1	Full	General		The Royal College of Nursing welcomes these draft guidelines. They seem appropriate. There is nothing further to add to this document.	Thank you for your comment.
Royal College of Physicians	1	Full	General		The RCP wishes to endorse the response submitted by the BTS	Thank you for your comment.
Royal Marsden and Royal Brompton Palliative Care Service	34	Full	General		We congratulate the guideline development group on their hard work. However, we do have some major concerns that essential elements related to the palliative care of these patients have been neglected in the guidelines. In addition key pieces of evidence related to symptom control in this group have been omitted. This may have been less likely to have occurred if there had been palliative care representation on your guideline group which we would consider essential. We have a specialist interest in the palliative care of IPF in this department and as previously stated in email correspondence, we would be happy to contribute and are in fact very keen to do so. We have looked at the full guidelines in detail and our concerns are detailed below.	Thank you for your comment. Adverts for GDG recruitment were posted on the NICE website and circulated to registered stakeholders in two separate occasions and no palliative care representation (consultant and/or nurse) was found at that time. With the agreement of NICE, the Chair of the guideline asked the two specialist nurses (with expertise in palliative care) on the GDG to also act as palliative care specialists for the GDG.
Royal Marsden and Royal Brompton Palliative Care Service	2	Full	18-19		For the Best supportive Care review questions we feel that symptom and improvements in psychosocial health should have been listed as critical outcomes alongside improvements in health related quality of life. The primary aims of best supportive care/palliative care are to improve symptom control (including psychosocial needs) and quality of life. It is not appropriate for them to be listed alongside outcomes such as hospitalisations due to IPF	Thank you for your comment. QOL is the critical outcome for Best Supportive Care, however the GDG have also considered symptoms and improvement in psychosocial health alongside improvements in health related quality of life.

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					complications or performance on sub-maximal walk test which have no relevance to best supportive care/palliative care.	
Royal Marsden and Royal Brompton Palliative Care Service	25	Full	170-171		Palliative care focuses on relieving suffering and achieving the best possible quality of life for patients and their carers. It involves the assessment and treatment of symptoms; support for decision making and assistance in matching treatments to informed patient and family goals; practical aid for patients and their carers; mobilisation of community resources to ensure a secure and safe living environment; and collaborative and seamless models of care across a range of care settings (i.e., hospital, home, nursing home, and hospice). Hospital and community palliative care is offered simultaneously with radical therapies for persons living with IPF. Comprehensive palliative care services integrate the expertise of a team of providers from different disciplines to address the complex needs of IPF patients and their families. Despite the availability of palliative care services for non-malignant patients the use of palliative care services by ILD clinicians for their patients remains low. Please see: Bajwah S, Higginson IJ, Ross JR, Wells AU, Birring SS, Patel A, Riley J. Specialist palliative care is more than drugs: a retrospective study of ILD patients. Lung 2012;190(2):215-20 Clinicians tend to perceive palliative care as the alternative to life-prolonging or curative care rather than as a simultaneously delivered adjunct to disease-focused treatment which can optimise the patient and carer journey.	Thank you for your comment. The GDG have considered the importance of palliative care services and input for people with IPF. These discussions have been captured in the 'linking evidence to recommendation' sections of the full guideline. Please see section 8.6 of the full guideline. Unfortunately, the study you have referenced was not included in our guideline for the following reason: Bajwah 2012 – this paper is not an intervention study and did not meet our inclusion criteria (please see appendix C for the guidelines evidence review protocols).

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					A clearer and more accurate description in your guideline of what palliative care is able to offer IPF patients and carers is needed to ensure that all stakeholders use palliative care appropriately optimising patient and carer quality of life. Palliative care has been shown to improve quality of life, mood and survival in lung cancer patients compared to standard chemotherapy treatment. Temel et 2010 NEJM Further research into the potential beneficial effects of palliative care in IPF are needed.	
Royal Marsden and Royal Brompton Palliative Care Service	29	Full	174-175		When discussing disease modifying treatments or radical treatments and their effects on dyspnoea sildenafil and bosentan were considered. However, a number of radical treatments were omitted. A full list of these radical interventions for IPF which assessed dyspnoea as an outcome measure may be found at: Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel A, Koffman J, Riley J. Interventions to improve symptoms and quality of life of patients with fibrotic ILD: a systematic review of the literature. December 2012 doi:10.1136/thoraxjnl-2012-202040	Thank you for your comment and for highlighting a systematic review, which we have cross checked for any relevant studies. The scope for this guideline stated which pharmacological interventions would be covered in this guideline. These included ambrisentan, azathioprine, bosentan, co-trimoxazole, mycophenolate mofetil, N-acetylcysteine, prednisolone, proton-pump inhibitors, sildenafil, warfarin and combinations of: prednisolone + azathioprine and prednisolone + azathioprine + N-acetylcysteine. We have considered the

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						studies mentioned in the systematic review you have references, against our inclusion criteria (please see appendix C for evidence review protocols) and are confident that all relevant studies to inform this evidence review have been retrieved.
Royal Marsden and Royal Brompton Palliative Care Service	30	Full	179-180		A number of studies which have used interventions in IPF to improve cough have been missed from your review. This include Lutherer et al. Please see the following for details: Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel A, Koffman J, Riley J. Interventions to improve symptoms and quality of life of patients with fibrotic ILD: a systematic review of the literature. December 2012 doi:10.1136/thoraxjnl-2012-202040	Thank you for your comment and for highlighting a systematic review, which we have cross checked for any relevant studies. We have considered the studies mentioned in the systematic review you have referenced, against our inclusion criteria (please see appendix C for evidence review protocols) and are confident that all relevant studies to inform this evidence review have been retrieved.
Royal Marsden and Royal Brompton Palliative Care Service	1	Full	17	18-20	All cause and IPF related mortality, survival and change in percentage predicted forced vital capacity are appropriate outcomes when considering radical interventions (disease modifying treatments) but they are not appropriate when considering palliative interventions (interventions that are aimed at symptom control and quality of life improving treatments). As this guideline is addressing management of IPF and an important part of that is the supportive care/palliative management, this is an important distinction	Thank you for your comment. The GDG considered appropriate to have a full range of outcomes, as best supportive care entails some interventions which may cause harm and best supportive care was not restricted to palliative care alone.

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					to make and very relevant when choosing appropriate outcomes. Please see the following published review for further details: Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel A, Koffman J, Riley J. Interventions to improve symptoms and quality of life of patients with fibrotic ILD: a systematic review of the literature. December 2012 doi:10.1136/thoraxjnl-2012-202040	We have considered the studies mentioned in the systematic review you have referenced, against our inclusion criteria (please see appendix C for evidence review protocols) and are confident that all relevant studies to inform this evidence review have been retrieved.
Royal Marsden and Royal Brompton Palliative Care Service	3	Full	19		In the Psychosocial support section improvements in psychosocial health (including depression) should have been listed in the critical outcomes alongside health related quality of life. In addition we feel that symptom control (not just dyspnoea) should have been an outcome eg there is often a complex interplay between anxiety and cough where anxiety may exacerbate cough.	Thank you for your comment. The psychosocial support evidence review was a qualitative review. The critical outcome to inform recommendations for this review was prioritised by the GDG to be health related quality of life. The GDG considered that outcomes such as dyspnoea and psychosocial health (including depression) were also important for decision-making and have been listed in the evidence review protocol which can be found in section 10.2.1 of the full guideline.
Royal Marsden and Royal Brompton	4	Full	19		In the Pulmonary Rehabilitation section all symptom relief should have been listed as an outcome. In the Swigris et al 2011 study, change in fatigue was	Thank you for your comment. The GDG agreed that the aim of pulmonary rehabilitation is to

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Palliative Care Service					measured. By limiting the outcome to change in cough and breathlessness, this data was not presented. Patients with IPF experience many symptoms in the last year and these are not limited to just dyspnoea and cough. Please see Bajwah S, Higginson IJ, Ross JR, Wells AU, Birring SS, Patel A, Riley J. Specialist palliative care is more than drugs: a retrospective study of ILD patients. Lung 2012;190(2):215-20	improve symptom relief and acknowledge that symptoms are not limited to dyspnoea and cough. In prioritisation of outcomes to be extracted in the review, the GDG considered overall quality of life and outcomes related to respiratory function such as dyspnoea (improvements in breathlessness) and sub maximal exercise testing to be of high importance in assessing the overall value of pulmonary rehabilitation. These outcomes were prioritised over individual measures and scales of fatigue at protocol stage by taking account of the following: • suspected variation in the tools used to measure fatigue led the GDG suspect data was less likely to be summarised in a manner useful to decision making. • The SF36, a tool to measure QoL and listed on the protocol, takes into account vitality and

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						therefore indirectly fatigue. • It was felt an overall picture of change in symptoms and related wellbeing as a result of pulmonary rehabilitation was best inferred by careful consideration QoL alongside measures of respiratory function. Therefore, the fatigue severity score as measured in the Swigris 2011 study was not prioritised as an outcome to extract for the review regarding pulmonary rehabilitation. For full list of outcomes please see section 8.2.1 of the full guideline. In addition, the study you have referenced was not included in our guideline because it is not an intervention study and did not meet our inclusion criteria (please see appendix C for the guidelines evidence review protocols and full list of outcomes).
Royal Marsden and Royal Brompton	5	Full	40	20	An important part of best supportive care/palliative care for these patients is to clarify end of life preferences should as preferred place of care (where they would like to be looked	Thank you for your comment. The GDG consider that this is adequately covered in

Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
Palliative Care Service					after at the end stages of their illness) and preferred place of death. This is rarely done: Bajwah S, Koffman J, Higginson IJ, Ross JR, Wells AU, Birring SS, Riley J. "I wish I knew more…." - the end-of-life planning and information needs for end-stage fibrotic interstitial lung disease: views of patients, carers and health professionals. BMJ Supportive & Palliative Care. 2012 September 2012. doi:10.1136/bmjspcare-2012-000263 And Bajwah S, Higginson IJ, Ross JR, Wells AU, Birring SS, Patel A, Riley J. Specialist palliative care is more than drugs: a retrospective study of ILD patients. Lung 2012;190(2):215-20	recommendation 1.5.5, which illustrates how as part of best supportive care, patient preferences should be considered when end of life discussions are to take place. Unfortunately, the studies you have referenced were not included in our guideline for the following reasons: Bajwah 2013 – this paper was published outside of our literature review cut-off date Bajwah 2012 – this paper is not an intervention study and did not meet our inclusion criteria (please see appendix C for the guidelines evidence review protocols).
Royal Marsden and Royal Brompton Palliative Care Service	6	Full	40	25	In managing an IPF patient with breathlessness at rest best supportive care/palliative care would be: • **Full assessment of breathlessness** • **Listening to fears, addressing negative feelings, exploring the meaning and significance of illness and symptoms** • **Management of panic and anxiety** • **Advice and teaching on coping strategies/use of complementary therapies** • **Use of non-pharmacological measures such as hand held fan.** Only if these measures were ineffective or the	Thank you for your comment. The GDG have considered the points you raise and recommendations 1.5.7 and 1.6.1 have now been amended to incorporate some of your suggestions. The GDG have provided guidance for people with IPF who are breathless at rest and therefore consider that these people require pharmacological interventions.

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					breathlessness was severe would we consider the use benzodiazepines and/or opioids.	
Royal Marsden and Royal Brompton Palliative Care Service	7	Full	42	32-44	At every review and follow up assessment of patients' symptom control and psychosocial needs should occur. If symptoms are not controlled or the respiratory physicians are struggling to control them, patients should be referred to the palliative care team. The palliative care team are able to offer brief interventions for patients with uncontrolled symptoms. Referral to palliative care should not be limited to advanced disease. In addition patients' information needs should be reassessed at every follow up and each consultation should include an assessment of the patients' wishes for treatment to ensure that respiratory clinicians are continuing treatment in line with patients' wishes. This may change over time and therefore needs reassessment at all follow up appointments: Bajwah S, Koffman J, Higginson IJ, Ross JR, Wells AU, Birring SS, Riley J. "I wish I knew more…." - the end-of-life planning and information needs for end-stage fibrotic interstitial lung disease: views of patients, carers and health professionals. BMJ Supportive & Palliative Care. 2012 September 2012. doi:10.1136/bmjspcare-2012-000263	Thank you for your comment. The GDG consider that the issues raised, such as assessment of symptom control and psychosocial needs are adequately covered in recommendation 1.6.1 as the consideration of referral to palliative care services is listed along with all the other clinical assessments that should be made at every follow-up appointment, such as the identification of exacerbations, referral to psychosocial services if required, assessment of comorbidities and lung function. Unfortunately, the study you have referenced was not included in our guideline because it was published outside of our literature review cut-off date.
Royal Marsden and Royal Brompton Palliative Care Service	8	Full	119		IPF patients and carers have clear unmet information needs. Patients and carers are very trusting that the respiratory physicians will deliver this information in a timely and effective manner. However qualitative work has shown that IPF patients and carers across 2 London	Thank you for your comment. The GDG have recognized this unmet information need in recommendations 1.3.1 and 1.3.3. .However, training

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					Hospitals had unmet information needs. Healthcare professionals across tertiary, secondary and primary care settings did not feel information was delivered effectively and more training was needed: Bajwah S, Koffman J, Higginson IJ, Ross JR, Wells AU, Birring SS, Riley J. "I wish I knew more…." - the end-of-life planning and information needs for end-stage fibrotic interstitial lung disease: views of patients, carers and health professionals. BMJ Supportive & Palliative Care. 2012 September 2012. doi:10.1136/bmjspcare-2012-000263	needs are to be decided at a local level. Unfortunately, the study you have referenced was not included in our guideline because it was published outside of our literature review cut-off date.
Royal Marsden and Royal Brompton Palliative Care Service	9	Full	120	15	See point 4 above	Thank you for your comment. Please see response in point 4 above.
Royal Marsden and Royal Brompton Palliative Care Service	10	Full	123		Kozu 2011- BDI/TDI is not listed and Qol tool used was SF-36 version 2 NOT SGRQ	Thank you for your comment. We have now corrected SQRG to state SF-36. However, BDI data was not given in the study and we have included evidence on the MRC dyspnoea score.
Royal Marsden and Royal Brompton Palliative Care Service	11	Full	124		Ozaveli 2010- Borg Dyspnoea Index not listed. Qol tool used was SF-36 Turkish version NOT SGRQ	Thank you for your comment. The study did not provide any figures for Borg index, but we have quoted MRCS and corrected SGRQ to SF-36
Royal Marsden and Royal	12	Full	124		Rammaert 2011- BDI not listed. Qol tool SF 36 and SGRQ not listed	Thank you for your comment. BDI was not listed in paper. No

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Brompton Palliative Care Service						outcomes in paper provided data for SF-36. We presented VAS as reported in paper.
Royal Marsden and Royal Brompton Palliative Care Service	13	Full	124		Swigris 2011- Outcomes not listed which should be: HADS and SF-36. In addition because of limited research question/outcomes included, Fatigue Severity Scale and Pittsburgh Sleep Quality Index have been excluded. For correct list of outcome measures for each intervention listed in points 10-13 please see the following paper and in particular appendix 4 online which lists the outcome measures used in each study: Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel A, Koffman J, Riley J. Interventions to improve symptoms and quality of life of patients with fibrotic ILD: a systematic review of the literature. December 2012 doi:10.1136/thoraxjnl-2012-202040	Thank you for your comment. The GDG agreed that the aim of pulmonary rehabilitation is to improve symptom relief and acknowledge that symptoms are not limited to dyspnoea and cough. In prioritisation of outcomes to be extracted in the review, the GDG considered overall quality of life and outcomes related to respiratory function such as dyspnoea (improvements in breathlessness) and sub maximal exercise testing to be of high importance in assessing the overall value of pulmonary rehabilitation. These outcomes were prioritised over individual measures and scales of fatigue at protocol stage by taking account of the following: • suspected variation in the tools used to measure fatigue led the GDG suspect data was less

Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						likely to be summarised in a manner useful to decision making. • The SF36, a tool to measure QoL and listed on the protocol, takes into account vitality and therefore indirectly fatigue. • It was felt an overall picture of change in symptoms and related wellbeing as a result of pulmonary rehabilitation was best inferred by careful consideration QoL alongside measures of respiratory function. Therefore, the fatigue severity score as measured in the Swigris 2011 study was not prioritised as an outcome to extract for the review regarding pulmonary rehabilitation. For full list of outcomes please see section 8.2.1 of the full guideline. In addition, the study you have referenced was not included in our guideline because it is not an intervention study and did not meet our inclusion criteria

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						(please see appendix C for the guidelines evidence review protocols and full list of outcomes).
Royal Marsden and Royal Brompton Palliative Care Service	14	Full	152		Relative values of different outcomes- see point 4 above.	Thank you. We have added clarification to the linking evidence to recommendation in section 7.6 of the full guideline section noting that quality of life scored encompassed a variety of domains, and expected the impact of other important outcomes such as fatigue to manifest in changes in quality of life scores.
Royal Marsden and Royal Brompton Palliative Care Service	15	Full	156		"the GDG discussed that the lack of IPF tailored pulmonary rehabilitation programmes may reflect variation in practice in the UK and therefore explain why there is no data examining the effect of different components of pulmonary rehabilitation". This is especially important when considering that a feature of pulmonary rehabilitation itself is to optimise the use of oxygen. This may be an important component which adds to any positive effects of pulmonary rehabilitation and until research into the individual components are done, it remains unclear what the exact effects of other aspects of pulmonary rehabilitation may be. Please see: Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel A, Koffman J, Riley J. Interventions to improve	Thank you. We have added a line to the quality of evidence in the linking evidence to recommendation section 7.6 of the full guideline recommendations to emphasise your point that the effect of individual components of rehabilitation is still unclear. A research recommendation for pulmonary rehabilitation was made to acknowledge further evidence would be beneficial. Please see research recommendation P6 in Appendix P.

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					symptoms and quality of life of patients with fibrotic ILD: a systematic review of the literature. December 2012 doi:10.1136/thoraxjnl-2012-202040	We have considered the studies mentioned in the systematic review you have referenced, against our inclusion criteria (please see appendix C for evidence review protocols) and are confident that all relevant studies to inform this evidence review have been retrieved.
Royal Marsden and Royal Brompton Palliative Care Service	19	Full	158	21-33	In addition an important part of best supportive care/palliative care for these patients is to clarify end of life preferences should as preferred place of care (where they would like to be looked after at the end stages of their illness) and preferred place of death.	Thank you for your comment. The GDG considered that when appropriate and as part of best supportive care, end of life discussions should be tailored to people's needs and preferences as indicated in recommendation 1.5.5.
Royal Marsden and Royal Brompton Palliative Care Service	20	Full	158	21-33	In addition an important part of best supportive care/palliative care for these patients is to assess and support the carers psychosocially. This disease impacts greatly on the carers and this aspect is not considered in your guideline.	Thank you for your comment. The GDG consider that this is appropriately captured in recommendations 1.3.1 and 1.3.3 by stating that information and support is to be given to people with IPF and their families and carers.
Royal Marsden and Royal Brompton Palliative Care Service	16	Full	158	10	Fatigue is acknowledged as a symptom which affects IPF patients but is not included in your outcomes measured when considering interventions relevant to best supportive care.	Thank you for your comment. Although we didn't specify fatigue as an outcome in our protocol we intended to use other outcomes, such as

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						reciprocal indicators of fatigue (i.e. vitality) as part of the interventions to assess palliation of fatigue as part of best supportive care. The GDG also considered that outcomes such as symptom relief that would encompass fatigue. Please see section 8.2.1 of the full guideline.
Royal Marsden and Royal Brompton Palliative Care Service	17	Full	158	11	Specialist palliative care both in the hospital and community are important.	Thank you for your comment. We agree.
Royal Marsden and Royal Brompton Palliative Care Service	18	Full	158	12	There is also the question of relationship of hypoxia and the sensation of breathlessness. There does not seem to a clear relationship between the two as it has been shown that occurrence of hypoxia (or absence of hypoxia) has no relationship to relief of breathlessness (Clemens et al 2008, Booth 2008). Therefore in delivering best supportive care i.e symptomatic relief of dyspnoea, clinicians should not become fixated on level of hypoxia as that may have no relation to the degree of dyspnoea experienced by the patient.	Thank you for your comment. The relevant recommendations on best supportive care have been amended for further clarification. Please see recommendations 1.5.6 and 1.5.7.
Royal Marsden and Royal Brompton Palliative Care Service	21	Full	158	37	Patients with IPF experience may symptoms in the last year of life which have not been listed in your search. Please see: Bajwah S, Higginson IJ, Ross JR, Wells AU, Birring SS, Patel A, Riley J. Specialist palliative care is more than drugs: a retrospective study of ILD patients. Lung	Thank you for your comment. The GDG agreed the clinically important outcomes in the evidence review protocol and the data for these outcomes has been presented in the guideline. These can be found

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					2012;190(2):215-20	in appendix C. Unfortunately, the study you have referenced was not included in our guideline because it is not an intervention study and did not meet our inclusion criteria (please see appendix C for evidence review protocols)
Royal Marsden and Royal Brompton Palliative Care Service	22	Full	159		Please see Point 2 above	Thank you for your comment. Please see response in point 2.
Royal Marsden and Royal Brompton Palliative Care Service	23	Full	159	15	This is incorrect- the Swigris 2011 study measured fatigue as an outcome. Please see: Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel A, Koffman J, Riley J. Interventions to improve symptoms and quality of life of patients with fibrotic ILD: a systematic review of the literature. December 2012 doi:10.1136/thoraxjnl-2012-202040	Thank you for your comment. The GDG agreed that the aim of pulmonary rehabilitation is to improve symptom relief. The GDG prioritised outcomes to be reviewed and placed greater importance to outcomes such as dyspnoea, sub maximal exercise testing and improvements in breathlessness. For full list of outcomes please see section 8.2.1 of the full guideline. We have considered the studies mentioned in the systematic review you have

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						referenced, against our inclusion criteria (please see appendix C for evidence review protocols) and are confident that all relevant studies to inform this evidence review have been retrieved.
Royal Marsden and Royal Brompton Palliative Care Service	24	Full	159	31	Allen 2005 also looked at the use of diamorphine for relieving dyspnoea in IPF patients which showed that there was an improvement in dyspnoea following administration of diamorphine and that it may improve anxiety. For details please see: Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel A, Koffman J, Riley J. Interventions to improve symptoms and quality of life of patients with fibrotic ILD: a systematic review of the literature. December 2012 doi:10.1136/thoraxjnl-2012-202040	Thank you for your comment. Allen 2005 was not an intervention study, and was therefore not included in the evidence review. We have considered the studies mentioned in the systematic review you have referenced, against our inclusion criteria (please see appendix C for evidence review protocols) and are confident that all relevant studies to inform this evidence review have been retrieved.
Royal Marsden and Royal Brompton Palliative Care Service	26	Full	171		In delivering best supportive care there needs to be a formal assessment of patients' symptom control and psychosocial needs and carers' psychosocial needs at each follow up. There is a danger that if there is no formal means of identifying unmet best supportive needs then these needs will fall by the way side in busy ILD clinics where the focus of management is often respiratory. In addition there is a danger that ILD clinicians may feel that they are adequately managing symptoms and	Thank you. We have amended the wording of recommendation 1.6.1 for greater clarification. Unfortunately, the study you have referenced was not included in our guideline because it is not an

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					psychological needs but in fact they are not. Please see the below paper that showed IPF patients had significant unmet palliative care needs in the last year of life: Bajwah S, Higginson IJ, Ross JR, Wells AU, Birring SS, Patel A, Riley J. Specialist palliative care is more than drugs: a retrospective study of ILD patients. Lung 2012;190(2):215-20 An appropriate outcome measure identifying unmet need may give an indication of the ILD and palliative care team set ups needed in each hospital ie different teams have different expertise (some ILD teams may be good at palliative care and not need strong palliative care input, but others may not- it is not satisfactory to assume that everyone is capable of delivering effective symptom control). However, until you assess this in terms of met and unmet needs, you cannot draw any conclusions. It is not adequate to just state anecdotally that needs are being met- there must be clear quantification and documentation.	intervention study and did not meet our inclusion criteria (please see appendix C for evidence review protocols)
Royal Marsden and Royal Brompton Palliative Care Service	27	Full	172		It is important that it is acknowledged that delivering end of life care and facilitating end of life conversations can be difficult for the health professional involved. ILD specialist nurses are not routinely trained in this area. If NICE is recommending that ILD specialist nurses lead in this area, we would recommend training and support specifically targeting this.	Thank you for your comment. Training specifications are outside of the scope of this guideline and are to be decided at a local level.
Royal Marsden and Royal Brompton	28	Full	174		Breathlessness is a complex multi-faceted symptom and is not just related to disease or co-morbidities i.e other aspects such as anxiety can cause and exacerbate	Thank you for your comment. The trade-off between the clinical benefits and harms are

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Palliative Care Service					breathlessness. Other potential harms of oxygen include that face masks can be intrusive and be perceived as a barrier by the family members between them and the patient.	discussed in the 'linking evidence to recommendations' in section 8.6 of the full guideline.
Royal Marsden and Royal Brompton Palliative Care Service	31	Full	180		The guideline recommends thalidomide as a treatment for cough "as there is no known alternative treatment for cough on the few occasions when it could be debilitating". We would like to draw the group's attention to the Ryan et al 2012 RCT article in the lancet looking at the use of gabapentin for refractory cough which showed it was effective in reducing intractable cough in a healthy population. Gabapentin is used routinely in our palliative care department with our IPF patients who have not responded to linctus or opioids. It is not free from side effects but certainly does not have the difficulties that thalidomide has attached to it. We would suggest that specific research into the use of gabapentin for cough in IPF patients is something that should be recommended by NICE.	Thank you for your comment. Ryan et al 2012 was not included in our evidence review because the study population included adults with refractory cough without active respiratory disease. The study did not look at patients with IPF, which is why it was not picked up using our search terms. Gabapentin was also not a intervention identified in the scope for this guideline. Due to the lack evidence retrieved to inform a recommendation the GDG used informal consensus to recommend that thalidomide could be discussed as a potential treatment option with patients' with IPF if their cough is retractable. The GDG felt that this was an area suitable for a research recommendation, as no

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						evidence for other potential drugs used in the treatment of cough were identified for use in patients with IPF. The GDG have also considered the points you raise and agreed that they are adequately covered in the research recommendation for cough. Please see recommendation P11 in appendix P.
Royal Marsden and Royal Brompton Palliative Care Service	32	Full	182		"much of the symptom relief is provided as part of best supportive care and that in the majority of cases the ILD teams will suffice" Please see point 26 above.	Thank you. We have amended the wording of recommendation 1.5.5 for greater clarification.
Royal Marsden and Royal Brompton Palliative Care Service	33	Full	182		We would advise changing McMillan Nurses to community palliative care nurses and adding palliative medicine doctors (including consultants) and spiritual care teams.	Thank you. The GDG feel this is now adequately covered in recommendations 1.5.10 and 1.6.1. Please also see section 8.6 of the full guideline where the GDG have outlined the composition of the palliative care team.
Sheffield Teaching Hospitals NHS Foundation Trust	1	Full	General	General	We find the guidelines clear and helpful	Thank you for your comment.
Sheffield Teaching	2	Full	General	General	We strongly endorse the patient-centred approach emphasised in the guidelines and also the clear proposal	Thank you for your comment.

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Hospitals NHS Foundation Trust					that specialist clinics are established, focussed on a strong multi-disciplinary team. We agree a dedicated MDT co-ordinator and, most importantly, a specialist ILD nurse are critical members of this team in addition to radiology, pathology and surgical colleagues	
Sheffield Teaching Hospitals NHS Foundation Trust	3	Full	General	General	We also strongly support the identification of some practical but important clinical research questions that could be addressed by a network of centres and MDTs contributing to randomised control trials and think it is refreshing that the guideline authors have identified a number of valuable studies that could be performed	Thank you for your comment.
Sheffield Teaching Hospitals NHS Foundation Trust	4	Full	General	General	It may be useful to mention secondary or traction bronchiectasis as a common complication of this condition, which might require specific consideration of sputum sampling and antibiotics.	Thank you. We have amended the wording of recommendation 1.6.1 for greater clarification.
Sheffield Teaching Hospitals NHS Foundation Trust	5	Full	General	General	No reference made to the management of exacerbations of IPF	Thank you for your comment. The searches for the drugs listed in the guideline scope did not yield any RCTs on management of exacerbations of IPF. The GDG also considered that non-drug options for acute exacerbations are restricted to symptom relief and that pulmonary rehabilitation is not appropriate for exacerbation.
Sheffield Teaching Hospitals NHS Foundation Trust	6	Full	General	General	The authors are clear that corticosteroids should never be used for attempting to prevent disease progression in IPF and we agree. Nonetheless there are occasional patients who are too elderly or unwell for surgical biopsy and who	The GDG acknowledge this point, however the care pathway of this guideline starts with suspected IPF and the

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					have a HRCT that is compatible with but not diagnostic of IPF, and in whom a trial of steroids for alternative diagnoses may be considered	treatment of IPF.
Sheffield Teaching Hospitals NHS Foundation Trust	7	Full	General	General	Unsure if the "do not use" approach is helpful. Perhaps it would be better reworded as "there is currently no evidence to support the use of the following, and clear evidence of harm in certain circumstances."	Thank you. The "do not use" recommendation is based on the available evidence and costs of the interventions. Further information to qualify recommendations, which state 'do not', can be found in the 'linking evidence to recommendations' sections, 6.11 and 10.6, of the full guideline.
The Royal College of Radiologists (in collaboration with the British Society of Thoracic Imaging)	1	Full	35	2 (table 19)	I would suggest specifying a consultant radiologist with an interest in interstitial lung disease	Thank you. This has now been amended within the table.
The Royal College of Radiologists (in collaboration with the British Society of Thoracic Imaging)	2	Full	43	1	"assessment for co morbidities" - might be helpful to expand this a bit. In particular repeat CT is indicated if there are clinical features to suggest new pathology such as malignancy, but not as part of routine follow up for IPF.	Thank you for your comment. The GDG consider the level of detail captured in recommendation 1.6.1 is sufficient.
The Society and College of Radiographers	1	Full	General		Does there need to be a differentiation between CT or CT High resolution with or without contrast? HRCT was mentioned but I was not clear whether this was	Thank you for your comment. CT has been used in the guideline to cover CT with or without contrast. We have

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					in the 1st instance and subsequent ones could be non contrast HRCT requires more specialised knowledge for reporting therefore there is an increased cost	explained this in the glossary and abbreviations of the guideline.

Inclusion and exclusion details table for comment 2 by Royal Brompton

ANTONIOU 2008	Intervention does not match protocol (study examines IPF outcomes in according to smoking status)
ATS2000	Retrieved by searches and studies referenced in this paper were obtained if relevant to protocol
ATS2011	Retrieved by searches and studies referenced in this paper were obtained if relevant to protocol
COLLARD2003	No relevant outcomes
CORTE2012	Population does not match protocol (includes IIP considered as IPF, NSIP and inter-determinate IIP; analyses not presented for IPF separately)
DEMEDTS2005	Included in pharmacological review
DUBOIS2011A	Included in prognostic evidence review
DUBOIS2011B	Included in prognostic evidence review
FLAHERTY2003	Population does not match protocol (fibrotic IIP -UIP and NSIP not distinguished)
HUNNINGHAKE2005	Not an intervention study
JEGAL2005	Population does not match protocol (fibrotic IIP, UIP and NSIP not distinguished)
KING2005	Intervention does not match protocol (interferon gamma)
LATSI2003	No relevant outcomes and population does not match protocol (UIP versus NSIP)
PANTHER2012	Included in pharmacological review
PEELEN2010	Population does not match protocol (fibrotic IIP, UIP and NSIP not distinguished)
RAGHU2012A	Included in pharmacological review
RICHELDI2012A	Included in prognostic evidence review
SCHMIDT2011	Included in prognostic evidence review
WELLS 1997	Analysis does not match protocol (univariable analysis only)
WELLS 2003	Population and analysis does not match protocol (cryptogenic fibrosing alveolitis univariable analysis only)
ZAPPALA2012	Included in prognostic evidence review