National Institute for Health and Care Excellence

Health Technology Evaluation

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis ID6446
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Action for Pulmonary Fibrosis	Appropriate	Comment noted. No action needed.
	Association of Respiratory Nurses	IPF/PPF are associated with high mortality and morbidity and treatment options are currently limited. There is a need for more evidence-based therapies so this evaluation is very welcome. A single technology appraisal is appropriate.	Comment noted. No action needed.
	Boehringer Ingelheim Ltd	The single technology appraisal route is appropriate for this topic.	Comment noted. No action needed.
	British Thoracic Society	It is appropriate to evaluate this topic as there remains a significant unmet clinical need for this group of patients.	Comment noted. No action needed.

Section	Stakeholder	Comments [sic]	Action
Wording	Action for Pulmonary Fibrosis	Yes	Comment noted. No action needed.
	Association of Respiratory Nurses	Wording is appropriate.	Comment noted. No action needed.
	Boehringer Ingelheim Ltd	Yes	Comment noted. No action needed.
	British Thoracic Society	Overall, the draft is well written, although there are two sections that would be good to review because they are not entirely clear: 'Subgroups' and 'Questions for consultation' (please see below). • idiopathic pulmonary fibrosis **and/or** progressive pulmonary fibrosis. We suggest the nomenclature of PF-ILD throughout and not use the term PPF as to use both is confusing.	Thank you for your comment. NICE's understanding is that progressive pulmonary fibrosis (PPF) was defined in the American Thoracic Society/ European Respiratory Society Japanese Respiratory Society/ Asociación Latinoamericana de Tórax (ATS/ERS/JRS/ALAT) clinical practice guideline. Before the publication of this guideline, the term 'progressive fibrosing interstitial lung disease

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			(PF-ILD)' had been described in clinical trial criteria and publications. Given the NICE recommendation for nintedanib in PF-ILD, we believe it is important to define PF-ILD in the background section of the scope. However, to help reduce confusion, we have amended the definitions of IPF and PPF to make it clearer that IPF and PPF are both forms of PF-ILD.
Additional comments on the draft remit	Action for Pulmonary Fibrosis	No comments	No action needed.
	Association of Respiratory Nurses	No comments	No action needed.
	Boehringer Ingelheim Ltd	No comments	No action needed.

Section	Stakeholder	Comments [sic]	Action
	British Thoracic Society	Use either PF-ILD (preferred) or PFF but not both	Comment noted. No further action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Action for Pulmonary Fibrosis	The information on symptoms and outcomes	Comment noted. No action needed.
	Association of Respiratory Nurses	- Both PPF and IPF require a diagnosis via MDT, not just IPF - Whilst chest pain can occur in ILDs, I would suggest that this is not one of the most common symptoms - Established clinical management for IPF extends beyond those listed and includes oxygen therapy as well as supportive, non-pharmacological care from a wider multidisciplinary team, including physiotherapists, occupational therapists, dieticians, nurses and psychologists.	Thank you for your comment and suggestions. We have included many of your suggested amendments and additions in the scope. Please note that the purpose of the background information is to provide a brief overview of the condition and it is not intended to be exhaustive.
	Boehringer Ingelheim Ltd	This provides an appropriate summary for a lay audience. We would suggest adding information to quantify the life-limiting nature of IPF and PPF using published literature such Gupta et al. 2024 and Simpson et al. 2021	Thank you for your comment. We have included information on

Section	Consultee/ Commentator	Comments [sic]	Action
			mortality from Gupta et al. 2024 and Simpson et al. 2021 in the scope.
	British Thoracic Society	Not all sarcoid causes ILD and/or PF ILD. Not all CTD causes ILD and/or PF ILD. It would be more accurate to state that PF-ILD can occur as a results of a variety of conditions which include, Sarcoidosis, CTD-ILD, Hypersensitivity pneumonitis and asbestosis. This reflects both clinical practice and the group studied in both the INBUILD and FIBRONEER. CTD -ILD be referred to as SARD-ILD (Systemic autoimmune rheumatic disease) to reflect the updated nomenclature as per the updated ACR guidelines from 2024. Would be useful to highlight the mechanism of action of nerandomilast and which pathogenic step it acts on versus other forms of treatment. Some revisions could be made to the section entitled 'Background section' - 1) The following sentence should be referenced – '*The most common symptoms are breathlessness (which may initially be only on exertion), cough, fatigue and chest pain'.* - 2) the sentence '*Sarcoidosis and connective tissue disease-associated ILD (CTD-ILD) are common types of PPF'* should be revised to say something like '*Sarcoidosis and CTD-ILD are common causes of PPF'* (as not all Sarcoid/CTD ILD leads to PPF). - While the incidence of Sarcoid and CTD-ILD are referenced it would be helpful to reference the incidence of Sarcoid/ CTD-ILD with PPF (which is highly relevant to the scope of the appraisal)	Thank you for your comment and suggestions. We have included many of your suggested amendments and additions in the scope. Please note that the purpose of the background information is to provide a brief overview of the condition and it is not intended to be exhaustive.

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		- Is there any reason why other potential causes of PPF are not mentioned eg Asbestosis/fibrotic hypersensitivity pneumonitis? - Would suggest that CTD -ILD be referred to as SARD-ILD (Systemic autoimmune rheumatic disease) to reflect the updated nomenclature as per the updated ACR guidelines from 2024?	
Population	Action for Pulmonary Fibrosis	Yes.	Commented noted. No action needed.
	Association of Respiratory Nurses	Yes	Commented noted. No action needed.
	Boehringer Ingelheim Ltd	Yes	Commented noted. No action needed.
	British Thoracic Society	Please see notes above	Commented noted. No action needed.
Subgroups	Action for Pulmonary Fibrosis	Subgroups seem to be appropriate	Commented noted. No action needed.
	Association of Respiratory Nurses	If possible, separate subgroup analysis of male and female subjects would help inform clinical decisions.	Thank you for your comment. Under the Public Sector Equality Duty in Section 149 of the Equality Act 2010, NICE is required to

Section	Consultee/ Commentator	Comments [sic]	Action
			advance equality of opportunity between people who share a protected characteristic and those who do not. As sex is a protected characteristic under the Equality Act 2010, it would not be appropriate for the committee to consider subgroup analyses based on sex alone.
	Boehringer Ingelheim Ltd	No comments	No action needed.
	British Thoracic Society	No relevant subgroups as both IPD and PF-ILD are well defined as per trial criteria, the latter defined as per disease behaviour. In subgroups, remove the FVC cut-off because that information does not provide anything.	Thank you for your comment. Stakeholders can provide input on the relevance of subgroups at the submission stage, and the committee may consider the relevance of subgroup analyses.
Comparators	Action for Pulmonary Fibrosis	Yes	Commented noted. No action needed.

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	Association of Respiratory Nurses	- Methotrexate may also be used - Oxygen therapy	Thank you for your comment. We have added methotrexate to the scope as a comparator because it was considered a current treatment for PF-ILD by clinical experts in NICE technology appraisal 747 (Nintedanib for treating progressive fibrosing interstitial lung diseases). Oxygen therapy may be used as part of best supportive care for some patients. Stakeholders are encouraged to submit evidence for which comparators they consider to be relevant to the evaluation. The committee will consider which comparators are relevant and how best supportive care is defined.

Section	Consultee/ Commentator	Comments [sic]	Action
	Boehringer Ingelheim Ltd	IPF No comments PPF Immunosuppressants, corticosteroids, infliximab and rituximab are not licensed for the treatment of PPF in the UK. Nintedanib is currently the only licensed treatment for PPF in the UK. It is anticipated that nerandomilast would be used in the same position as nintedanib in the care pathway (as add-on treatment to standard care) and as such, immunosuppressants, corticosteroids, infliximab and rituximab would be used concomitantly with nerandomilast. Therefore, nerandomilast is not expected to replace these treatments and, as such, they do not meet the definition of a comparator as per the NICE process and methods. It should also be noted that these treatments were discussed as part of TA747, and it was agreed that immunosuppressants, corticosteroids, infliximab, and rituximab were not considered appropriate comparators for nintedanib. Before the introduction of nintedanib, the treatment options available were used solely to alleviate symptoms and manage other aspects of the underlying disease. There is no evidence that these treatments slow the progression of pulmonary fibrosis. Clinical advice indicates that where these treatments are used, there are specific reasons related to the underlying cause and are used concurrently with nintedanib. Immunosuppressants are used to treat the inflammatory component of the disease for some patients. For example, infliximab may be used to manage the underlying rheumatological condition, but there are no	Thank you for your comment. We note that nerandomilast could be positioned as an add-on therapy to standard care. However, immunosuppressants, corticosteroids, infliximab and rituximab were identified by clinical experts in NICE technology appraisal 747 (Nintedanib for treating progressive fibrosing interstitial lung diseases) as current treatment for PF-ILD. Therefore, these therapies may be relevant comparators for this evaluation. Stakeholders are encouraged to submit evidence for which comparators they consider to be relevant to the evaluation. The committee will consider which comparators are appropriate.

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		clinical trials or guidelines that support its use in PPF. Where such treatment is considered appropriate, it is used concomitantly with nintedanib. In summary, we believe the appropriate comparators in PPF to be: • Nintedanib • Best supportive care	
	British Thoracic Society	Define best supportive care as this is the comparator – BTS quality standards.	Thank you for your comment. Stakeholders are encouraged to submit evidence for which comparators they consider to be relevant to the evaluation. The committee will consider which comparators are relevant and how best supportive care is defined.
Outcomes	Action for Pulmonary Fibrosis	Yes, although there are significant quality of life related issues associated with currently approved antifibrotic therapies, that are not drawn out in blunt tools used to assess quality of life and should be considering thoroughly by the committee.	Thank you for your comment. The committee will consider all evidence submitted by stakeholders, including evidence on the impact of the condition on patients and carers. The committee will also consider any benefits of

Section	Consultee/ Commentator	Comments [sic]	Action
			the technology that are not captured in the QALY calculation. In line with section 4.3 of the NICE manual, the EQ-5D is the preferred method to measure health-related quality of life in adults given the need for consistency across evaluations. However, in some circumstances the EQ-5D may not be the most appropriate measure. Paragraphs 4.3.10 to 4.3.12 of the NICE Manual provide information on how stakeholders can make a case that the EQ-5D is inappropriate.
	Association of Respiratory Nurses	Yes. This is a comprehensive list, which I'm pleased to see includes several patient-centred measures.	Comment noted. No action needed.
	Boehringer Ingelheim Ltd	Progression in IPF and PPF is measured using decline in forced vital capacity (FVC). Separate measures of progression such as progression-free survival are not used in IPF and PPF and, as such, were not included as an outcome	Thank you for your comment.

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		in the FIBRONEER trials. Therefore, we do not expect to include evidence on this outcome in the submission and do not believe that this is an appropriate outcome measure. While lung transplantation could be considered a marker for progression of lung disease, it is not relevant for this patient population. Clinical experts advise that only 3% of patients with IPF or PPF would be eligible. In summary, we suggest that these two outcomes (progression-free survival and lung transplantation) are removed from scope.	We have removed progression-free survival as an outcome from the scope based on feedback that disease progression in IPF and PPF is defined by decline in lung function. We have kept lung transplantation as an outcome in the scope because it may be an important outcome for consideration even if a small proportion of patients may be eligible for it.
	British Thoracic Society	Define physical function. Define how health related QOL will be measured.	Thank you for your comment. Physical function may be measured using a variety of outcome measures.. Stakeholders can provide evidence for which outcome measures are most

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			relevant in their submissions. In line with section 4.3 of the NICE manual, the EQ-5D is the preferred method to measure health-related quality of life in adults given the need for consistency across evaluations.
Equality	Action for Pulmonary Fibrosis	n/a	No action needed.
	Association of Respiratory Nurses	As above, male and female outcomes may vary and should be considered seperately, if possible.	Thank you for your comment. Under the Public Sector Equality Duty in Section 149 of the Equality Act 2010, NICE is required to advance equality of opportunity between people who share a protected characteristic and those who do not. As sex is a protected characteristic under the Equality Act 2010, it

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			would not be appropriate for the committee to consider subgroup analyses based on sex alone.
	Boehringer Ingelheim Ltd	No comments.	No action needed.
	British Thoracic Society	Nintedanib capsules contain gelatin which is not acceptable to some e.g. Halal. Is the the outer coating of this medication different and if so this would be important to highlight from an EDI perspective.	Comment noted. The committee will consider any relevant equalities issues in its deliberations.
Other considerations	Action for Pulmonary Fibrosis	No comments	No action needed.
	Association of Respiratory Nurses	No comment	No action needed.
	Boehringer Ingelheim Ltd	No comments	No action needed.
	British Thoracic Society	No comments	No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Questions for consultation	Action for Pulmonary Fibrosis	*Where do you consider nerandomilast will fit into the existing care pathway for idiopathic pulmonary fibrosis and progressive pulmonary fibrosis?* Given the increased efficacy and significantly reduced adverse events (which are a factor that sees 40% of patients stop taking current therapies), we would hope that clinicians would have access to this treatment first line with adjuvant therapies as required. *To what extent does the definition of 'progressive pulmonary fibrosis' align with the definition of 'progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis'?* The definition of PPF has been set out by the European Respiratory Society. What is considered best supportive care for idiopathic pulmonary fibrosis? Supportive services for PF have been outline in the OneVoiceILD care pathway. What is considered best supportive care for progressive pulmonary fibrosis? As above Please select from the following, will nerandomilast be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): None of the abovev. Nerandomilast will be prescribed only in specialist settings, as antifibrotic prescribing in ILD is organised through specialised services and the Clinical Reference Group for Specialised Respiratory. Currently this is only available for patients considered by the 23 ILD specialist centres in England.	Thank you for your comments. No action needed.

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		For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. n/a Do you consider that the use of nerandomilast can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? As many as 40 percent of patients on current antifibrotic therapies have to cease taking the treatment due to intolerabilityunwieldly side-effects. This may be picked up in part through HRQoL metrics but this should be considered carefully. This organisation has recently collected data relating to patient preferences around antifibrotics and will include in the subsequent NICE consultation.	
	Association of Respiratory Nurses	*To what extent does the definition of 'progressive pulmonary fibrosis' align with the definition of 'progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis'?* I think both are accurate definitions *To what extent do the comparators listed in the scope reflect established clinical management?* I think they are reflective, taking into account my comment above What is considered best supportive care for idiopathic pulmonary fibrosis? *Access to a multidisciplinary team to allow symptom support with issues like breathlessness, fatigue, weight loss, frailty and psychological distress as well as support with issues such as benefits, carer support and end-of-life planning.*	Thank you for your comments. No action needed.

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		What is considered best supportive care for progressive pulmonary fibrosis? *As above* Please select from the following, will nerandomilast be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care *C. Prescribed in secondary care with routine follow-up in secondary care* D. Other (please give details): For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. *Mostly within secondary care, although supportive care may be delivered in the community or via organisations like local hospices.* Would nerandomilast be a candidate for managed access? *It may be relevant to have this on a named patient basis for patients who have not tolerated alternative antifibrotics and are, for example, awaiting lung transplantation.*	
	Boehringer Ingelheim Ltd	**Where do you consider nerandomilast will fit into the existing care pathway for idiopathic pulmonary fibrosis and progressive pulmonary fibrosis?** <u>IPF</u> The existing care pathway for IPF patients is described in CG163 (represented in Figure 1 below).	Thank you for your comments. No action needed.

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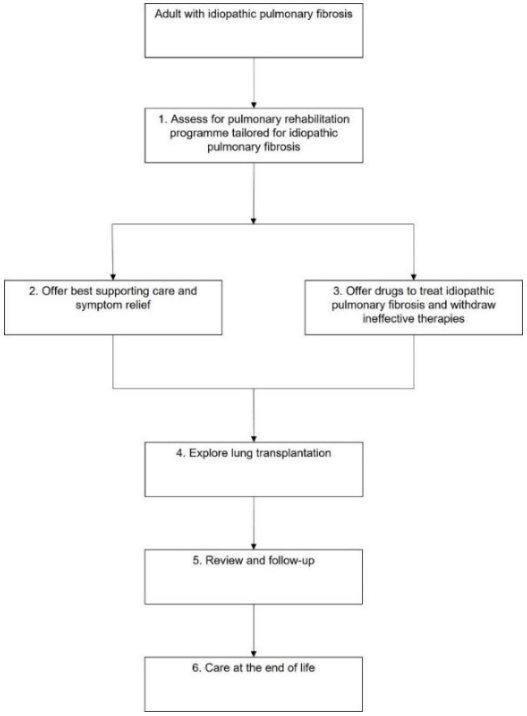
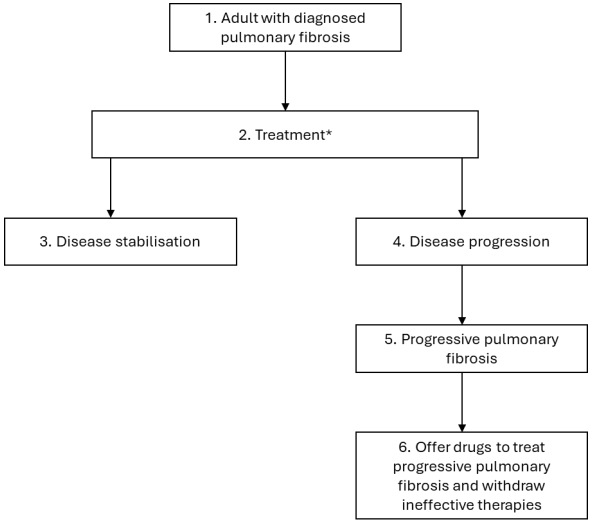
		It is anticipated that nerandomilast would be used in Part 3 (offer drugs to IPF and withdraw ineffective therapies). The proposed change would allow initiation of nerandomilast from the point of diagnosis, or when deemed appropriate by the treating physician. *Figure 1: Current clinical pathway of care for IPF*  	

		PPF Clinical guidelines are not available for PPF; however, a similar care pathway has been drawn below (see Figure 2). It is anticipated that nerandomilast would be used in Part 6 (offer drugs to treat PPF and withdraw ineffective therapies). The proposed change would allow initiation of nerandomilast from the point of confirmation of progressive disease, or when deemed appropriate by the treating physician. *Figure 2: Current clinical pathway of care for PPF*  	

Section	Consultee/ Commentator	Comments [sic]	Action
		*Conventional treatments based on the specific form of pulmonary fibrosis, including, but not limited to corticosteroids, mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate and rituximab **To what extent does the definition of 'progressive pulmonary fibrosis' align with the definition of 'progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis'?** PPF aligns very closely with the definition of "progressive fibrosing interstitial lung excluding IPF". PPF was defined in 2022 in the American Thoracic Society/ European Respiratory Society Japanese Respiratory Society/ Asociación Latinoamericana de Tórax [ATS/ERS/JRS/ALAT] guidelines; before this, the term progressive fibrosing interstitial lung disease (PF-ILD) had not formally been defined in guidelines, but had been described in previous clinical trial criteria and publications. Both PPF and PF-ILD are described as fibrotic interstitial lung disease that show evidence of progression. In the PPF guidelines, this progression is defined according to certain parameters including respiratory symptoms, physiological parameters (FVC and diffusing capacity of the lung for carbon monoxide [DLco]) and radiological progression, as assessed over 1-year follow up. In previous clinical trials including the INBUILD study and the FIBRONEER-ILD study, patients with progressive fibrosis were defined according to predefined criteria (a combination of respiratory symptoms, FVC decline, and radiological progression) within 24 months before screening; 87.2% of patients within the FIBRONEER-ILD trial were documented to also meet the criteria for PPF defined in the 2022 ATS/ERS/JRS/ALAT guidelines, demonstrating a close alignment between both definitions.	

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		To what extent do the comparators listed in the scope reflect established clinical management? These reflect established clinical management apart from the comments made in the 'Comparators' section related to immunosuppressants, corticosteroids, infliximab and rituximab. **What is considered best supportive care for idiopathic pulmonary fibrosis?** As described within clinical guideline CG163: 1. Information and support 2. Symptom relief 3. Management of comorbidities 4. Withdrawal of therapies suspected to be ineffective or causing harm 5. End of life care. Depending on symptoms, ambulatory or long-term oxygen therapy may also be considered. **What is considered best supportive care for progressive pulmonary fibrosis?** Clinical guidelines in PPF are not available; however, these are assumed to be the same as for IPF. **Please select from the following, will nerandomilast be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care**	

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		D. Other (please give details): C The capacity constraints, resource limitations, and geographic dispersion of tertiary centres present significant challenges for many patients. The integration of ILD services and the delegation of specialised conditions aims to address these challenges, ensuring equitable access and localised care for individuals with rare diseases. The availability of nerandomilast in secondary care, under the oversight of ILD specialists, is a crucial component of realising the 10 year health plan and alignment with model region imperatives. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** Does not differ **Would nerandomilast be a candidate for managed access?** The FIBRONEER trials form the main evidence base for nerandomilast. These are robust, multinational randomised controlled trials with additional follow-up data up to 76 weeks. Therefore, it is not anticipated that nerandomilast would be a candidate for managed access. However, we are open to discussing managed access should this be required. **Do you consider that the use of nerandomilast can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Early initiation of nerandomilast, as soon as it is deemed appropriate by the treating physicians, is highly important for patients. A recent national survey	

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		of individuals with IPF and PPF suggests that a diagnosis of these conditions causes more shock and anxiety than a diagnosis of cancer, highlighting the psychological trauma of receiving a diagnosis of IPF or PPF. In addition, patients face significant quality-of-life burden due to difficulties in accessing specialised care, treatment, and follow-up. These aspects are difficult to quantify and include in the quality-adjusted life year (QALY) calculation.	
	British Thoracic Society	No comments	No action needed.
Additional comments on the draft scope	Action for Pulmonary Fibrosis	No comments	No action needed.
	Association of Respiratory Nurses	No comments	No action needed.
	Boehringer Ingelheim Ltd	No comments	No action needed.
	British Thoracic Society	No comments	No action needed.