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Research Protocol

Treatments for idiopathic pulmonary fibrosis: a systematic review and economic evaluation

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1. Title of the project:

The clinical and cost effectiveness of treatments for idiopathic pulmonary fibrosis: a systematic review and economic evaluation.

2. Name of team and project 'lead'

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3. Plain English Summary

IPF is a serious lung disease, the exact cause of which is not known. It generally affects people over 60 years of age and the main symptom is shortness of breath, which can have a considerable impact on day to day life. IPF was once thought to progress at a steady, predictable rate, but this is often not the case. Many people with IPF deteriorate rapidly, while others have periods of relative stability. In general people with IPF survive between two to five years. Evidence shows that the number of people with IPF is increasing, although the reasons for this are unclear.

IPF is a difficult condition to manage, particularly in the latter stages, and people with IPF experience a poor quality of life. People with IPF often become very breathless and frequently have a dry cough. As a consequence this can also lead to difficulties undertaking activity and a heightened sense of

anxiety. Treatments aim to reduce symptoms and improve survival. The type of treatment offered can vary, and people with IPF can also vary in their response to the available treatments. A number of new treatments for IPF have emerged over recent years. Of all the treatments now used in practice it is uncertain which are effective and provide the best value for money to the NHS. There are some existing systematic reviews which evaluate some of these treatments individually, but these do not investigate all of the treatments now available, and do not evaluate both clinical effectiveness and cost effectiveness. We have undertaken searches of the medical literature and found a number of new studies of treatments for IPF that need to be considered in our research.

We aim to bring together the most up-to-date, high quality, published and unpublished evidence on the benefits, harms and costs of treatments for IPF. The results of our study will be helpful to patients and carers and also to health care professionals treating IPF. We will disseminate our findings through a final report and through submission of papers to relevant conferences and journals.

4. Background

4.1.1 Description and epidemiology of idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a debilitating respiratory condition for which there is no cure. It is characterised by diffuse scarring (fibrosis) and mild inflammation of the lung tissue leading to a gradual worsening of lung capacity. IPF is a difficult condition to manage, particularly in the latter stages, and people with IPF experience a poor quality of life. The epidemiology of IPF is uncertain but recent estimates suggest that between 10- 20 in every 100,000 adults are affected by IPF,[1;2] with approximately 4.6 in every 100,000 developing IPF each year.[3] This suggests that between 5000 and 10000 adults in the UK may suffer from IPF at any one time with some 2000 new cases each year. The number of cases appears to be increasing, although the reasons for this are unclear. Data from primary care suggest that the number of IPF cases rose progressively between 1991 and 2003 and that this was not attributable to the diagnosis of milder cases or an increase in the age of the population during this time.[3] IPF is known to affect males more than females and in particular affects those in middle age, with two-thirds aged over 60 years at presentation.[3] Factors associated with the condition, for which there is no known cause, include cigarette smoking, environmental exposure, and possibly infective agents.

IPF is classed as an idiopathic interstitial pneumonia, which is a group of interstitial lung disease (ILD) also known as diffuse parenchymal lung disease. The definition of IPF was revised by international consensus statements published in 2000 and 2002 following the identification of a new subgroup with substantially better survival.[4;5] These guidelines stated that the terms IPF and cryptogenic fibrosing alveolitis (CFA) are synonymous,[5] although the British Thoracic Society used the term ‘CFA clinical

syndrome' to correspond to a characteristic clinical presentation seen typically in IPF but common also in other idiopathic interstitial pneumonias.[6] Distinguishing IPF from other idiopathic interstitial pneumonias can be difficult as presentation can be similar. However, the consensus statements[4;5] provide differential diagnostic criteria. A further consensus statement is currently anticipated which aims to simplify the diagnosis further.

4.1.2 Impact of the condition

The natural history of IPF is not fully understood. IPF is a progressive chronic condition which leads to a decline in lung function which culminates in respiratory failure and death.[7] IPF was once thought to progress at a steady, predictable rate, but this is often not the case, with many people deteriorating rapidly and others having periods of relative stability in their condition.[8] Mean survival is estimated to be between 2-5 years from diagnosis. Pulmonary assessments may be useful to predict survival, however, at present the prognosis for an individual patient remains difficult to define.

Presentation is often due to a gradual onset of shortness of breath on exertion. This non specific symptom can be wrongly attributed to the ageing process, or a respiratory tract infection, and therefore diagnosis can often be made some time after initial presentation.[8] In others IPF is an incidental finding on a routine chest examination. Key symptoms of IPF include breathlessness (dyspnoea), a non-productive cough, which can be paroxysmal (spasmodic) in nature, reduced exercise tolerance, and anxiety. The irritating dry cough associated with IPF has a significant impact on a patients life, leading to a reduced quality of life.[7] Over the course of the illness these symptoms progressively worsen and become more debilitating and disabling to the patient. In some people unexpected deterioration can occur with a sudden worsening of symptoms and resultant hypoxemia (decreased partial pressure of oxygen in blood).[8] These episodes are usually without clinically apparent infection, or other identifiable cause. Known as 'acute exacerbations', these are thought to occur in about 10-14% of cases and can be terminal episodes.[9] Another common complication of IPF is pulmonary hypertension which has a significant impact on outcome.

Patients with IPF are frequently admitted to hospital and hospices, although accurate data is scarce as many studies have small sample sizes. One recent study undertaken in the USA followed 168 patients over a 76 week period and found 23% of these were hospitalised for respiratory related illnesses on 57 occasions.[10] The mean number of days stay in hospital was 15 days, with the most common reason for hospitalisation being suspected infection. Data from the UK suggests that in 2008/9 there were 9,500 finished consultant episodes for people categorised as 'other interstitial pulmonary diseases with fibrosis' with around 600 hospital admissions.[11] The mean length of stay for these people was nine days. In addition to high admission rates, patients with IPF can also require costly treatments over a prolonged period of time. For example, the approximate cost over one year for a patient requiring 24-

hour oxygen, via an oxygen concentrator (including electricity which is paid for by the NHS, but excluding the cost of the equipment) with a portable oxygen cylinder for back-up, could be in the region of £2000. Access to effective and cost effective treatments could potentially help to reduce hospital admissions and reduce length of hospital stays.

4.1.3 Current treatment options

There is no national guidance for the treatment of IPF and no universally accepted best treatment for IPF. In addition no therapy has yet been established to improve survival or modify significantly the clinical course of IPF. Several treatment options are currently available to clinicians. The British Thoracic Society, Thoracic Society of Australia and New Zealand and the Irish Thoracic Society recently published a practice guideline[6] on interstitial lung disease, which included recommendations for the treatment of IPF. The publication points out that many patients with advanced IPF have received suboptimal care in the past and provides not only details of potential treatment strategies for those with IPF, but stresses the importance of early recognition of terminal decline and liaison with palliative care specialists.

There are a number of potential treatments for IPF, however with an often inconsistent evidence base of the different treatments available, there is variation in practice in the UK. The aim of treatment is generally to reduce symptoms and prolong survival, however treatment responses are thought to vary considerably. A number of new treatments have been proposed in recent years. Symptomatic treatments available include oxygen therapy, opioids, corticosteroids and anti-reflux therapy. In some cases pulmonary rehabilitation, which includes exercise, education and psychological support is given. Disease-modifying treatments include immunosuppressants (such as azathioprine and cyclophosphamide), antifibrotics (such as interferon gamma-1b and bosentan), anti-inflammatory drugs with antifibrotic effect (e.g etanercept); antifibrotic agents that interfere with collagen synthesis (such as pirfenidone, colchicine and penicillamine), antioxidants (e.g N-acetylcysteine) alone or in combination. Other proposed treatments include thalidomide for intractable cough and treprostinil, sildenafil and ambrisentan for pulmonary hypertension associated with IPF. In some cases lung transplantation is considered.

No evidence synthesis of the clinical and cost effectiveness of these treatments has been undertaken, and evidence syntheses of other treatments are also in need of updating (see below). According to the British Thoracic Society, ‘with regard to IPF in particular, the last 3 years have seen more studies of treatment that in the previous history of the speciality, yet there is no universally accepted “best current treatment”.[6]

5. Planned investigation

5.1 Research aim and objectives

The proposed research will undertake a systematic review and decision analytic model comparing the clinical and cost-effectiveness of the different treatment strategies used within the NHS for IPF.

The main objectives will be as follows:

1) To conduct a systematic review of the clinical and cost effectiveness of treatments for IPF.

2) To adapt an existing economic model or construct a de novo model for the UK to estimate the cost effectiveness of the different treatments.

3) To identify deficiencies in current knowledge and to generate recommendations for future research.

5.2 Methods for synthesis of evidence of clinical effectiveness

A systematic review of the evidence for clinical-effectiveness will be undertaken following the general principles outlined in Centre for Reviews and Dissemination (CRD) report 'Undertaking Systematic Reviews of Research on Effectiveness' (Third edition)[12] and the PRISMA statement on the reporting of systematic reviews and meta-analyses.[13] This review will update and expand on the existing systematic reviews, to ensure the full range of treatments currently used are considered for this evaluation of the clinical and cost effectiveness of treatments for IPF.

Search strategy

Literature will be identified from several sources including electronic databases, bibliographies of articles, grey literature sources and hand searching of specialist journals. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager software. Searches to identify studies will be carried out via a number of routes:

1) General health and biomedical databases including MEDLINE, EMBASE, Science Citation Index, BIOSIS;

2) Specialist electronic databases: CRD, the Cochrane library;

3) Grey literature and conference proceedings;

4) Contact with individuals with an interest in the field;

5) Checking of reference lists;

6) Research in progress databases: UKCRN website, Current Controlled Trials (CCT), Clinical trials.gov, ICTRP.

All databases will be searched from inception to the current date, there will be no language restrictions. Literature will also be identified from bibliographies of articles, grey literature sources, and consultation with experts.

Study Selection

Studies will be selected for inclusion through a two-stage process using the predefined and explicit criteria. The full literature search results will be screened independently by two reviewers to identify all citations that may meet the inclusion criteria. Full manuscripts of all selected citations will be retrieved and assessed by two reviewers against the inclusion criteria. Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken. An inclusion flow-chart will be developed and used for each paper assessed. Any disagreements over study inclusion will be resolved by consensus or if necessary by arbitration by a third reviewer.

The criteria for study inclusion in the systematic review are as follows:

Intervention	Available interventions which aim to manage symptoms or modify the disease (including but not restricted to oxygen therapy, opioids, corticosteroids, immunosuppressants, antifibrotic agents and pulmonary rehabilitation). Our clinical experts and advisory group will be asked to identify the current treatments used in the UK to ensure that the key treatments in use are included in the review.
Participants	People with a confirmed diagnosis of IPF.[†]
Comparators	Potential comparators include any of the interventions, best supportive care and placebo interventions.
Outcomes	Outcomes will include survival, measures of symptoms (breathlessness, cough), quality of life, lung function/capacity, exercise performance, adverse events, costs and cost-effectiveness. Patient assessed subjective outcome measures will be included if assessed by validated tools.
Design	Randomised Controlled Trials (RCTs). Where no RCTs are identified for a particular intervention, Controlled Clinical Trials (CCTs) with a concurrent control group will be eligible. Cost effectiveness studies which measure costs and consequences will be eligible for the review of cost effectiveness

[†]As there has been a change in the diagnostic criteria for IPF, particular attention will be paid to the inclusion criteria used by studies to ensure that the results are not influenced by mixed populations with differing prognoses. Studies of mixed populations will be included if the study report outcomes for those with IPF separately.

Data extraction and quality assessment

The extraction of studies' findings will be conducted by two reviewers using a pre-designed and piloted data extraction form to avoid any errors. The methodological quality of all included studies will be appraised using recognised quality assessment tools[12] and criteria for appraising economic evaluations.[14;15] Where possible, missing information will be obtained from investigators. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

Data synthesis

Studies will be synthesized through a narrative review with tabulation of results of included studies. Where possible the results from individual studies will be synthesized through meta-analysis, with causes of heterogeneity of results examined. The specific methods for meta-analysis and for the detection and investigation of heterogeneity will depend upon the summary measure selected.

If required, a sensitivity analysis will be conducted for studies where the definition of IPF is unclear.

Pulmonary hypertension is a complication of IPF which can have a significant impact on outcome. The presence of pulmonary hypertension will not be a reason for exclusion in our proposed research. We will discuss the presence of pulmonary hypertension in any included studies in the narrative of our review, and where data permits will explore the presence of pulmonary hypertension as a subgroup.

In addition, a mixed treatment comparison (MTC) will be considered. This will allow ranking of the effectiveness of the range of treatments being evaluated. MTC is an extension of traditional, pairwise, meta-analysis where a statistical analysis of the network of trial evidence is used to produce comparable estimates of benefits and harms for a range of treatments. The feasibility and appropriateness of a MTC will be explored and the MTC conducted if appropriate using current guidance on good practice.

5.3 Methods for synthesis of evidence of cost effectiveness

The cost-effectiveness of treatments for IPF will be assessed through two stages: a systematic review of cost effectiveness studies and the development of a decision analytic economic model.

Searches of general biomedical databases (as listed in section 2.4), specialist databases (e.g. NHS Economic Evaluation Database), unpublished literature and conference proceedings will be carried out to identify relevant studies. Studies will be included in the systematic review if they are full economic evaluations (cost effectiveness, cost utility or cost benefit analyses) that report both measures of costs and consequences. The methodological quality of included studies will be assessed using accepted criteria for appraising economic evaluations.[14] Studies will be synthesised through a narrative review that includes a clear explanation of the assessment process, detailed critical appraisal of study methods, critical assessment of data used in any economic models and tabulation of the results of included studies.

Existing economic models of interventions for the management and treatment of IPF, identified in the systematic review of economic evaluations, will be assessed for their quality, relevance and suitability for adoption in the current review. If no relevant high quality economic evaluations are identified, a *de novo* decision analytic model will be developed. Accepted guidelines for good practice in decision-analytic modelling and the general principles outlined in the NICE 'reference case' will be followed.[15;16] Development of the structure and parameters of the model will be informed by several sources including previous models identified in the systematic review of cost effectiveness, evidence on the epidemiology, natural history of IPF, clinical pathways and the likely impact of alternative management strategies, as well as guidance from clinical and methodological advisors. The model will be validated through discussion with expert advisors. The model will be populated with best available evidence: clinical effectiveness parameters will be taken from the systematic review of clinical evidence, as will information on adverse events and complications associated with included interventions. Additional targeted literature searches will be required to populate other parameters in the model as necessary.

If targeted searches fail to identify appropriate utility estimates for patients with IPF or associated complication/ comorbidity we will attempt a mapping exercise. This will involve:

1. searching for studies reporting HRQoL data for patients with IPF that can be transformed or mapped onto a utility scale (for example, using the method reported by Ara and Brazier (2008)[17] to convert mean SF-36 dimension scores to mean EQ-5D preference-based scores)
2. identifying, in collaboration with relevant experts, conditions that may be considered similar to IPF for which there are published utility estimates
3. if both of the above methods fail to identify appropriate estimates we would use elicitation techniques to derive utility estimates from an expert panel (including, but not necessarily limited to the project advisory group) using health state descriptions.

Where expert opinion has been used, this will be clearly identified in the report of the model. The model description will clearly indicate the place in the evidence hierarchy for data entering the model,[18] particularly as evidence of effectiveness may come from studies with a range of designs.

The model will provide a cost-consequence analysis, reporting the costs of alternative interventions for the management and treatment of IPF and their consequences in terms of patient outcomes (including symptom reduction, acute exacerbations, avoiding hospitalisation, quality of life and impacts on life expectancy, where relevant). It will adopt a UK NHS and Personal Social Services perspective with cost and outcomes discounted at an annual rate of 3.5%. The model will present cost effectiveness estimates in terms of incremental cost per quality adjusted life year (QALY) gained.

The resource use for providing interventions will be estimated from studies included in the systematic review of clinical effectiveness, published costing studies identified by our searches, any relevant clinical guidelines and from discussion with expert advisors.

As far as is possible costings developed for the model will proceed by first identifying and quantifying resource use – from studies included in the clinical effectiveness, the cost effectiveness review or targeted searches for resource use/ costing studies – and then applying appropriate unit costs. The items of resource use identified from published sources and the estimated quantities used will be discussed with clinical experts (in the context of mapping the care pathway) to assess their comprehensiveness and appropriateness. Where resource use data from published literature is insufficient we would use estimates from relevant clinical experts and this will be clearly identified in the final report. To develop unit cost estimates we will assess official, nationally-representative sources (NHS Reference Costs,[19] Unit Costs of Health and Social Care,[20] British National Formulary[21]) for applicability and level of detail, as well as unit cost estimates applied in studies included in the systematic review of cost effectiveness and in costing studies identified by cost effectiveness searches. If these sources are inadequate we would develop unit cost estimates in collaboration with the costing unit at Southampton University Hospitals NHS Trust. Costs will be inflated to current prices using the Hospital and Community Health Services Pay and Prices Index, where necessary.[20]

The report will clearly indicate the sources for input data to the model and will also clearly indicate the study types from which the input data were derived (and where those study designs sit in the conventional evidence hierarchy). Sensitivity analyses and scenario analyses will be conducted with respect to variables over which there is greatest uncertainty. For the deterministic analyses this will be oriented toward variables with the greatest uncertainty over their methods of derivation or where choices/ judgments have had to be made between alternative sources. The key variables to be explored in sensitivity/ scenario analyses will include: clinical effectiveness parameters (including any assumptions regarding the presence or duration of any disease modifying effects of treatment), cost of interventions and health related quality of life estimates included in the model. The importance of the underlying model assumptions will be assessed through an analysis of different scenarios, particularly where evidence to populate the model is inadequate or conflicting (for example where the model uses data derived using expert opinion). The results of the probabilistic sensitivity analysis will be presented using cost effectiveness acceptability curves (CEACs). Where considered appropriate, value of information analysis will be undertaken to help inform payback in terms of reduced parameter uncertainty from additional research, identifying which parameters most contribute to decision uncertainty and should therefore be the focus of future research.[22;23]

The model will be developed using standard software, such as MS Excel and TreeAge Pro, to ensure transparency and will be flexible in terms of permitting different estimates for key input parameters. All model assumptions and data sources will be clearly specified and their effects on outcomes checked through sensitivity analysis, to ensure model results accurately reflect the inputs used. Internal consistency will also be assessed through the replication of the model in different software to compare results. External consistency will be assessed through comparing results with the previously published analyses.

6. Advisory group

Representatives and other potential users of the review from different professional backgrounds and opinions, including academics, clinicians, health economists, commissioners, patient groups, and professional organisations, will be invited to provide expert advice to support the project. In addition, we will invite a member of the Guideline Development Group to the NICE guideline on IPF to join the advisory group. The NICE guideline is on the diagnosis and initial assessment of IPF and we believe our proposed work will be a useful compliment to the guideline for patients and clinicians. All of our expert advisors will be asked to provide comments on a version of the protocol and of the draft final report, as well as advising on the identification of relevant evidence for both the clinical and cost effectiveness elements of the propose research. Involving people with different perspectives with the opportunity to comment on any potential biases will help to ensure an independent assessment is undertaken. All experts will be asked to register competing interests and to keep the details of the report confidential.

At the beginning of the project representatives from service users will be invited to join the advisory group to inform the review. They will be asked to provide comments on a version of the protocol and of the draft final report. There are a number of potential UK societies such as the British Lung Foundation and the Pulmonary Fibrosis UK support group who will be approached. All service users will be asked to register competing interests and to keep the details of the report confidential.

7. Competing interests of authors

None declared.

8. Key milestones

Milestones	**Date**
Project Initiation	
Development and peer review of protocol	May 2012
Formation of advisory group	May 2012
Literature searching and study retrieval	May - June 2012
Assessment of studies for inclusion	June – August 2012

Milestones	Date
Assessment of study quality	August – September 2012
Data extraction	August – October 2012
Data synthesis	October – November 2012
Mixed treatment comparison	November – December 2012
Develop model structure	October – November 2012
Data collection	November – January 2013
Perform modelling scenarios and sensitivity analysis	January 2012 – February 2013
Drafting of final report	February – March 2013
Updating of searches and systematic review	March 2013
Peer review and updating of report	March – April 2013
Submission and dissemination of report	End April 2013

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