Study protocol

CHARACTERISING PATIENT PATHWAYS TO THE DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS: REAL WORLD DATA STUDY

An exploratory historical database study characterising patient pathways to diagnosis of IPF, identifying and quantifying blocks and red flags through primary, secondary, and tertiary care settings.

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TITLE	Characterising Patient Pathways to the Diagnosis of Idiopathic Pulmonary Fibrosis: Real World Data Study
Subtitle	An exploratory historical database study characterising patient pathways to diagnosis of IPF, identifying and quantifying blocks and red flags through primary, secondary, and tertiary care settings.
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Marketing authorisation number	NA
Study aims and objectives	**Study aim**: To explore the real life clinical pathways and feasibility of characterising pathways towards diagnosis of idiopathic pulmonary fibrosis (IPF) using real-world data. **Primary objective**: To characterise patients' pathways (through primary and secondary care records) from the first adult symptoms and clinical features suggestive of IPF to the date of diagnosis of IPF. **Secondary objective**: To identify the blocks (disruptions to patients' pathways) and red flags that may highlight ways to reduce time to IPF diagnosis in IPF patients and potential IPF patients
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1.0 Background

Idiopathic pulmonary fibrosis (IPF) is the most common and lethal of the idiopathic interstitial pneumonias. It is estimated to affect between 14–43 people per 100,000, most commonly occurring in those over the age of 50.[1-3]

The disease appears to be driven by abnormal/dysfunctional alveolar epithelial cells that promote fibroblast recruitment and proliferation. The result is scarring of the lung, irreversible loss of function and decreased oxygen to the major organs of the body.[4;5] It has an associated 5- year survival of approximately 20%.

The diagnosis of IPF is based on the absence of a known cause of lung fibrosis, computed tomography (CT) findings and, in cases with CT abnormalities that are not classical for IPF, the use of pathological criteria.[6] Diagnostic uncertainties, partly due to the multiple different ways in which physicians approach IPF (e.g. the availability of appropriate lung biopsy specimens and accurate medical histories) along with the variability in the natural history of disease and in HRCT appearances; and the lack of a validated algorithm for excluding known causes of lung fibrosis all contribute to the inherent confusion surrounding IPF diagnosis.[7] An IPF diagnosis requires an integrated multidisciplinary approach involving pulmonologists, radiologists, and pathologists and establishing an accurate diagnosis can be challenging.[6;7]

Until recently, treatment options for patients with IPF have been limited, primarily focusing on symptom management and palliation. Yet growing understanding of the pathogenesis of the disease over the last two decades has resulted in the development of novel compounds targeted at the mechanisms underlying the disease pathobiology. Indeed in 2014, the European Medicines Association (EMA) in Europe and Food and Drug Administration (FDA) in the USA approved two “first-in-class” compounds (pirfenidone and nintedanib) for the management of IPF.[8-11] Both drugs have pleiotropic mechanisms of action and have been shown to slow disease progression and lung function decline in IPF patients with mild to moderate functional impairment. There are also data to suggest they reduce the risk of acute exacerbations, which can lead to hospitalisation and death.[4;12] A recent update of the ATS/ERS/JRS/ALAT clinical practice guideline on IPF treatment, also have made conditional recommendations for use of these novel agents.[13]

The arrival of these new agents place increased emphasis on the need for earlier identification and diagnosis to optimise potential treatment benefits. At this time, knowledge is limited of the pathway to a diagnosis of IPF. In absolute terms, IPF is a rare condition that affects only a very small number of patients. Clinicians working in general practice may only come across one or two cases in their medical careers. As such, it is likely that patients presenting in primary

care with symptoms of IPF may be misdiagnosed and that there may be a delay in their IPF diagnosis.

In the UK, all patients who ultimately receive a diagnosis of IPF will have first presented in the primary care setting. Thus by carrying out a historical review of the primary care records for patient in the years preceding their IPF diagnosis, it should be possible to identify common patterns (trends) in healthcare resource utilization (HRU) and identify potential "red flags" to support decision support tools to aid earlier diagnosis. This study aims to characterise the pathways to diagnosis of IPF.

2.0 Study aim and objective

2.1 Study aim

To explore the real life clinical pathways and feasibility of characterising pathways towards diagnosis of idiopathic pulmonary fibrosis (IPF) using real-world data.

2.2 Study objective

Primary objective: To characterise patients' pathways (through primary and secondary care records) from the first adult (age ≥ 18 years) symptoms and clinical features suggestive of IPF to the date of diagnosis of IPF.

Secondary objective: To identify the blocks (disruptions to patients' pathways) and red flags that may highlight ways to reduce time to IPF diagnosis in IPF patients and potential IPF patients. Red flags are defined as features, signs and symptoms in a patient which indicate development of IPF based on thorough review of the patient pathway.

3.0 Study design

3.1 Study design

The study will be a historical cohort study using electronic medical records and linked questionnaire data from the Optimum Patient Care Research Database (OPCRD). In a study sub-population, secondary and tertiary care referral data reviewed by OPC from in-practice data will be additionally analysed.

3.2 Study period

The study period will include the 47-year period (1970-2017) coincident with the migration of UK patient records from paper to electronic format.

(A) Patients with an IPF diagnosis code

The evaluation period will consist of:

a. An index date, defined as the date of first IPF diagnosis[a] (specific or broad definition Read codes) if patients were:

   - Diagnosed with IPF on or before 1st May 2017

b. Characterising patients' pathways (through the primary and secondary care setting) to IPF diagnosis from the time of their first symptoms and clinical features (as an adult) suggestive of IPF to the index date, based on the following:

   - Electronic Health Records (EHR);
   - De-identified free text data captured in general practice;
   - De-identified referrals data e.g. clinic letters from secondary and tertiary centres

[a] The date of first IPF diagnosis will be determined using a database algorithm. This set of rules will be developed from the qualitative pilot study and will be used to identify patients in OPCRD who are highly likely to have an IPF diagnosis.

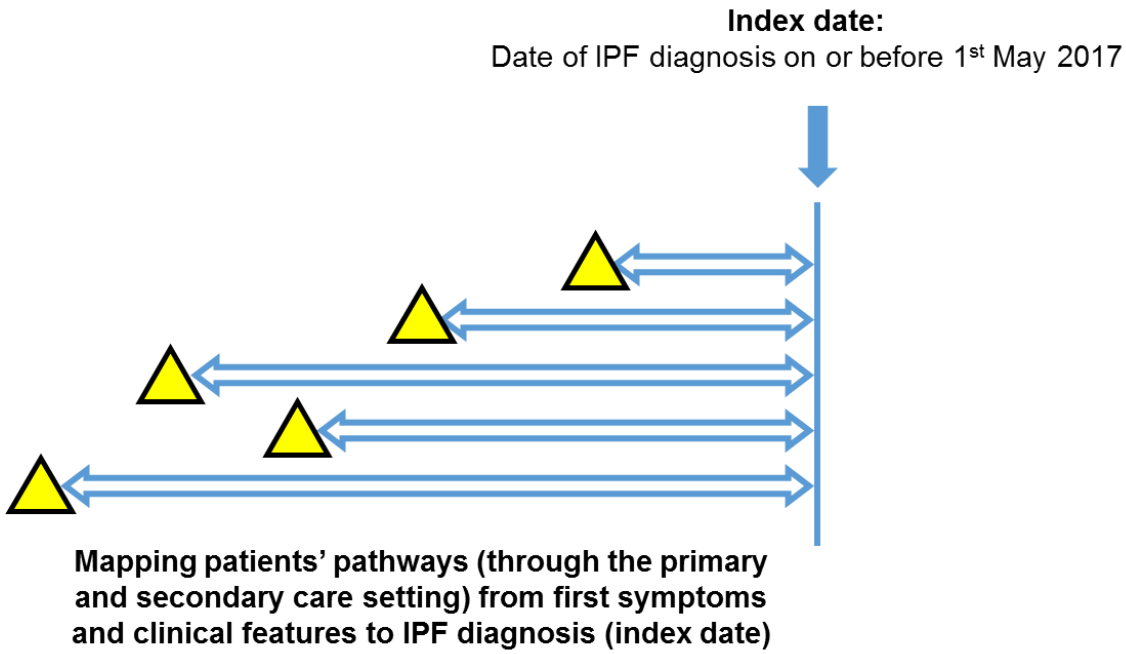

Figure 1: Study design for patients with an IPF diagnosis code

(B) Potential IPF patients (identified based on treatment suggestive of IPF)

The evaluation period will consist of:

a. An index date, defined as the date of most recent treatment suggestive of IPF (from Read codes or free text), on or before 1st May 2017

b. Evaluating patients' records for potential missed diagnoses/diagnosis codes of IPF by identifying symptoms and clinical features suggestive of IPF, reverse-chronologically from the index date, based on the same data sources listed in Study Population (A) Patients with a coded IPF diagnosis

[Options: In addition to (A) and (B), the following options are simultaneously being explored to identify definite IPF patients:

1) Identifying patients who are prescribed IPF treatment from the NHS Blueteq Drug System
2) The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary Fibrosis with the addition of Co-trimoxazole EME-TIPAC RCT (via Andrew Wilson)

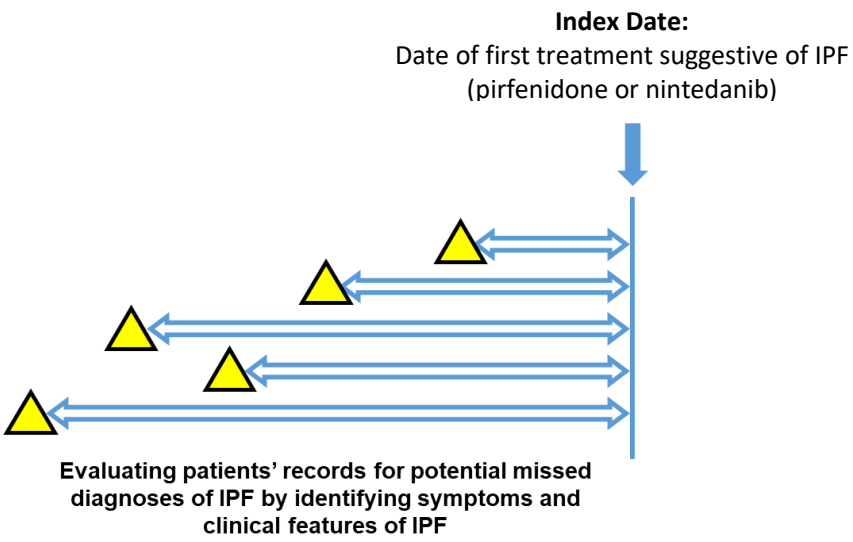

Figure 2: Study design for potential IPF patients

4.0 Study population

4.1 Inclusion and exclusion criteria for Study Population (A) Patients with an IPF diagnosis code

Inclusion criteria for Study Population (A) Patients with an IPF diagnosis code

The study will be conducted in 2 stages: (1) Qualitative pilot study and (2) Quantitative full study. All patients must fulfil the following inclusion criteria:

1. A diagnostic Read code for IPF (specific or broad definition) on or before 1st May 2017:

- Specific codes: Idiopathic fibrosing alveolitis (H563.), Cryptogenic fibrosing alveolitis (XE0Yb), Idiopathic fibrosing alveolitis NOS (H563z), Usual interstitial pneumonitis (H5633 or X102v), Alveolar capillary block (H5630);
- Broad codes: Diffuse pulmonary fibrosis (H5631), Pulmonary fibrosis (H5632), Hamman-Rich syndrome (XE0Zr).

2. ≥1 year of continuous data prior to the index date
3. Age ≥30 years at index date

Patients included in stage (2) Quantitative full study must fulfil the addition criterion:

4. Determined to be highly likely to have an IPF diagnosis based on database rules developed from the pilot qualitative study

Exclusion criteria

Patients with concomitant diagnostic Read codes[b] (Read code lists in Appendices 1-2) for the conditions below will be excluded after a manual review of records.

- Sarcoidosis
- Allergic alveolitis
- Pneumoconiosis
- Asbestosis
- Other causes of pulmonary fibrosis

As this is an exploratory study, a manual review will be conducted to ascertain that IPF patients were not incorrectly coded before excluding these patients.

Table 1: Inclusion and exclusion criteria for Study Population (A) Patients with an IPF diagnosis code

[b] Published in Navaratnam, V., et al. "The rising incidence of idiopathic pulmonary fibrosis in the UK." *Thorax* 66.6 (2011): 462-467

4.2 Inclusion and exclusion criteria for Study Population (B) Potential IPF patients identified based on treatment suggestive of IPF

Inclusion criteria for patients identified for Study Population (B) Potential IPF patients identified based on treatment suggestive of IPF

The study will be conducted in 2 stages: (1) Qualitative pilot study and (2) Quantitative full study. All patients must fulfil the following inclusion criteria:

1. Patients prescribed with therapy suggestive of IPF: pirfenidone or nintedanib (Read code list and free text search terms listed in Appendix 6)
2. ≥1 year of continuous data prior to the index date
3. Age ≥30 years at index date

Patients included in stage (2) Quantitative full study must fulfil the addition criterion:

4. Determined to be highly likely to have an IPF diagnosis based on database rules developed from the pilot qualitative study

Table 2: Inclusion and exclusion criteria for Study Population (B) Potential IPF patients identified based on treatment suggestive of IPF

4.3 Data source

Optimum Patient Care Research Database (OPCRD)

OPCRD is a longitudinal healthcare database developed, maintained, and owned by Optimum Patient Care (OPC), a social enterprise company that aims to improve patient outcomes through medical research and provision of evidence-based, patient centred clinical services. OPCRD currently comprises anonymised electronic health records for over 3.5 million patients, from over 600 primary care practices across the UK. OPC extract de-identified data from all primary care clinical systems, and are capable of capturing the majority of patients at a given practice participating in the OPC Clinical Review Services. OPCRD contains two types of data: (1) routinely recorded electronic health records and (2) patient reported outcomes from 50,000 respiratory questionnaires. OPC can also undertake initiatives involving review of in-practice data including secondary care referral data and links with secondary care data and nationwide practice prescribing data to enable targeted delivery of specific dataset needs.

The database has received a favourable opinion from the NHS Health Research Authority for anonymous research use (REC reference: 15/EM/0150). Governance is provided by the

Anonymised Data Ethics and Protocols Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG, http://www.effectivenessevaluation.org/) to govern the standard of research conducted on internationally recognised databases.

5.0 Study variables and study outcomes

5.1 Demographic and baseline variables

1. Demographic & lifestyle factors (at or closest to index date):

    - Sex
    - Age
    - Height
    - Weight
    - Body mass index, (BMI)
    - Smoking status

2. Comorbidities: evidence as (i) coded diagnoses and (ii) implied by drug prescriptions:

    - Respiratory (recorded ever prior to index date)

        a) COPD: presence of comorbid COPD; duration of comorbid COPD; date of diagnosis of COPD
        b) Asthma: presence of comorbid asthma; duration of comorbid asthma; date of diagnosis of asthma
        c) Chronic respiratory conditions other than asthma and COPD: presence of comorbid condition; duration of condition

    - Other (recorded ever prior to index date)

        a) Allergy (eczema, allergic or non-allergic rhinitis), active/non-active definitions
        b) Nasal polyps
        c) Diabetes mellitus
        d) Gastroesophageal reflux disease (GERD), active/non-active definitions
        e) Ischemic heart disease (IHD)
        f) Heart failure
        g) Anxiety/depression, active/non-active definitions
        h) Charlson Comorbidity Index
        i) Cancers of the respiratory tract

3. IPF diagnosis codes

    - Number of repeated IPF diagnosis codes

5.2 Primary outcome – characterisation of patient pathway to IPF diagnosis

Patient pathways to IPF diagnosis will be characterised from the period starting at the first symptoms and clinical features suggestive of IPF up to IPF diagnosis date using pathway

features. Pathway features will not be defined *a priori* but defined and standardised after an exploratory, qualitative review of a subgroup of patients. The quality and consistency of data recording of IPF diagnoses and of pathway features will also be evaluated during the qualitative stage. These findings will be used to refine methods used to summarise pathways during the quantitative analysis stage subsequently.

1. Blocks (i.e. disruptions to the ideal pathway) in the pathway to IPF diagnosis

The different pathways characterised will be compared to the ideal pathway. Blocks will be identified and quantified as delays (additional time spent) in the pathway due to the blocks. Examples of blocks are: time spent in primary care, incorrect diagnosis (such as COPD, severe asthma, or heart failure), and misinterpretation of spirometry.

2. Red flags prior to IPF diagnosis:

Red flags are features, signs and symptoms in a patient that indicate development of IPF. Similarly, pathways will be compared to the ideal pathway to identify red flags. Examples of red flags are: COPD diagnosis with non-obstructive spirometry and significant breathlessness, severe 'COPD' symptoms without a smoking history, very fast treatment escalation, hypoxia and/or oxygen therapy without proper diagnosis/misdiagnosis.

5.3 Study variables – pathway features to characterise patient pathways to IPF diagnosis

Only pathway features that are recorded with adequate quality and consistency (evaluated during the qualitative stage) in the database will be defined as study variables used to systematically characterise pathways in the full study population. The list of study variables will be finalised after the qualitative review stage but ***examples*** of pathway features (variables) that could be defined are:

1. Clinical history/presentation
   - Dyspnoea on exertion
   - Dry cough
   - Hiatal hernia
   - Gastroesophageal reflux disease (GERD)
   - Fatigue and weight loss
   - Family history
     - Pulmonary fibrosis
     - Interstitial lung disease

2. Physical examination
   - Inspiratory crackles
   - Extremity exam for finger clubbing
   - Signs of connective tissue disease (to rule out CTD & rheumatologic disease)

3. Modified Medical Research Council (mMRC) dyspnea score

4. COPD assessment test (CAT) score (where available)

5. Chest imaging
   - Chest x-ray
   - High-resolution computed tomography (HRCT)

6. Standard laboratory assays

7. Serologic tests (to rule out connective tissue diseases)

8. Pulmonary function testing
   - Total lung capacity (TLC)
   - Forced vital capacity (FVC)
   - FEV_1/FVC ratio
   - Transfer factor (DL_{co})
   - 6-minute walk test

9. Bronchoscopy
   - Bronchoalveolar lavage
   - Transbronchial biopsy

10. Surgical lung biopsy

11. Pharmacotherapy prescriptions
    - Respiratory pharmacotherapy prescriptions:
      - Short-acting bronchodilators
      - Long-acting bronchodilators
      - Inhaled corticosteroids
      - Other respiratory therapies (e.g. LTRA, theophylline, biologics)

    - Antibiotics
      - All prescriptions
      - Prescribed with respiratory consultation or hospitalization

    - All other pharmacotherapy prescriptions

12. Health care encounters and referrals

    - Respiratory consultations (outpatient): primary care, secondary care and tertiary specialist IPF centre setting

    - Hospitalisations (in-patient attendances)

    - A&E attendances

    - Referrals to more specialized respiratory care settings: secondary care,
      - Tertiary specialist IPF centre

6.0 Data analysis plan

6.1 Overview of data analysis plan

Data will be analysed in two stages:

1) An exploratory, qualitative review in a subset of the full study population using:
    a. Read codes and free text in medical records by primary care clinicians recorded in OPCRD; AND
    b. Secondary and tertiary care referral data, including anonymised, scanned clinic letters from specialists and free text, from OPC's review of in-practice data
2) A quantitative, descriptive summary of the full study population using Read codes and free text in OPCRD only

6.2 Exploratory, qualitative review of a study sub-population

The qualitative review stage will include a pilot study, followed by the full qualitative review.

(I) Pilot study

A pilot study of two patient subsets will be sampled initially for the exploratory, qualitative review stage of the study:

a) Patients coded with an IPF diagnosis (minimum n=20 patients): referral data and OPCRD data (free text and Read codes) will be reviewed; and
b) Potential IPF patients, identified based on treatment suggestive of IPF: OPCRD data (free text and Read codes) only will be reviewed.

according to the inclusion criteria specified in Section 4.1

The objective of the pilot study is to develop database rules (algorithm) that can be used to systematically identify patients from OPCRD who are highly likely to have an IPF diagnosis. In the pilot study, information from referral data (e.g. clinic letters, respiratory reports, etc.) will be manually reviewed and used to validate IPF diagnoses. Among patients with a validated IPF diagnosis, database features will be identified (e.g. patients coded with an IPF diagnosis code at least twice), and database rules will be developed. These rules will allow the quantitative full study to be conducted using OPCRD data by including only patients who are highly likely to have IPF and to determine the date of first IPF diagnosis.

(II) Full qualitative review

Additional patients coded with an IPF diagnosis beyond the pilot study will by sampled by convenience sampling for the qualitative review. Referral data and OPCRD data will be reviewed.

The objectives of the qualitative review are:

1) Describe the first symptoms and clinical features suggestive of IPF and explore the feasibility of identifying first codes suggestive of IPF

Patient records will be reviewed reverse-chronologically from the date of diagnosis to identify the first symptoms and clinical features suggestive of IPF. For example, the first prescription of respiratory pharmacotherapy, the first respiratory complaint, first recorded spirometry values, or non-respiratory features including fatigue, weight loss, and finger clubbing.

These symptoms and features will be described, and the feasibility of developing an algorithm to identify the first codes suggestive of IPF in the larger study population will be explored.

The algorithm will be developed by compiling code lists (for Read codes) and words lists (for free text data) of the most commonly used codes/words associated with the identification of the first codes suggestive of IPF. The algorithm will be tested by applying it to a further 100 patients (beyond the qualitative review subpopulation) in the overall larger study population, and the percentage of patients for which the algorithm accurately identifies the first codes suggestive of IPF will be calculated.

2) Identify and qualitatively describe the following:
    a) Pathways to IPF diagnosis (describe pathway features from first-respiratory code to IPF diagnosis)
    b) First symptoms and clinical features suggestive of IPF
    c) Potential blocks in pathways
    d) Red flags in pathways

3) Develop code and word lists for items 3a-3d (above) to enable data extraction and standardised analysis in the full study population

To enable data extraction and standardised data analysis in the full study population, code lists (for Read code data) and word lists (for free text data) of the most commonly used codes and words associated with items 3a-3d above (pathway features, clinical presentation at the first respiratory code, blocks and red flags in pathways) will be compiled during the qualitative review stage. The consistency and quality of data recording in OPCRD will also

be evaluated to ensure the appropriateness of data extraction as study variables for the full study population.

6.3 Quantitative summary of pathways to IPF diagnosis, blocks and red flags

Data will be extracted for variables defined by the code and word lists for the full study population. For continuous variables, mean, standard deviation, median, inter-quartile range, minimum and maximum will be reported, as appropriate. For categorical variables, frequencies and percentages will be reported.

Occurrence of all symptom and code combinations in the 1-year period up to the index date will be displayed in a co-occurrence table. Principal component analysis (PCA) will then be performed to visualize prevalence and co-occurrence of signs and symptoms occurring in a 90 days and 365 days period prior to diagnosis. This approach can visually represent natural groupings based on the underlying structure of the data.

Code frequency for signs and symptoms in the years prior IPF diagnosis will be generated and expressed as rate per 100 patient-years with 95% confidence interval. Time-course of signs, symptoms and weight measurements at the individual patient level will be plotted to visualize the disease progression patterns leading to the IPF diagnosis.

Furthermore, blocks will be quantified in terms of delay (time spent) in the pathway compared to the ideal pathway. An example ideal patient pathway to IPF diagnosis is shown in Table 1. This style of reporting will be repeated for the other occurring pathways from first respiratory code to diagnosis, in order to identify blocks and red flags in primary, secondary and tertiary care.

Table 1: Example output to quantify pathways

	Patient presents to GP	GP investigates crackles, spirometry, mMRC score	Patient gets chest imaging e.g. chest X-ray, CT	Patient is referred to a secondary care chest consultant	Patient referred to a tertiary care specialist IPF centre	IPF investigated by multi-disciplinary team and diagnosis made
Number of patients, n (%)						

Time from date of first respiratory code, median (IQR)						
Time from date of first respiratory code,, 5th, 95th centiles						

6.4 Feasibility counts

(A) Patients with an IPF diagnosis code

In an earlier study including IPF patients up to year 2015 from the OPCRD database,[1] 1,480 and 743 patients were included under the broad and specific cohorts respectively.[c] Compared to this study, the current study includes patients from age of 30 and above, and does not have an inclusion criteria for the first diagnosis received after 1990. As such, and due to additional 1 year 5 months of data (up to May 2017), the current study is expected to include more than 1,480 and 743 patients in the broad and specific cohorts respectively.

(B) Potential IPF patients (identified based on treatment suggestive of IPF)

(Patients prescribed pirfenidone or nintedanib: 15 patients were identified to be prescribed pirfenidone from a read code and free text search of the whole of OPCRD. No patients were prescribed nintedanib. 11 out of these 15 patients had an IPF diagnosis code (i.e. would be included in Study Population A). 4 patients (in the whole of OPCRD) would be identified as a "potential IPF patient" based on this criterion.

7.0 Regulatory and ethical compliance

Ethical approval will be sought from ADEPT. This study was designed and shall be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the

[c] 2016 Respiratory Effectiveness Group study "Opportunities for earlier IPF diagnosis". Inclusion criteria in this study were: diagnosis code for IPF, first diagnosis received after 1990, age ≥ 40 years at index date. Exclusion criteria was: prior diagnosis of connective tissue disease, sarcoidosis, allergic alveolitis

ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu.

8.0 Data dissemination

Results from the full study findings will be submitted via an abstract to a target conference.

9.0 Advisory group

The steering committee members are:

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- Dr Robina Coker, Imperial College London robina.coker@imperial.ac.uk

10.0 Research team

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11.0 Timelines

Activity	Date
Contract Signature	Contract signature
Steering Committee Engagement	23 June 2017 (or 1 week post Contract signature)*
Data procurement (part 1: pilot 30 patients)	7 July 2017
Delivery of Pilot Analysis	15 September 2017
Delivery of Final Protocol	18 December 2017 (v2.2)
Abstract for ERS 2018	15 February 2018
Data procurement (part 2: full patient cohort)	1 May 2018*
Delivery of Full Dataset, comprising: 1. OPCRD Data (Read codes & free text) 2. Linked Blueteq prescribing data	1 June 2018*
Abstract for BTS 2018	June 2018
Delivery of Final Analysis and Study Report	1 July 2018*

* Detailed timelines to be communicated to Roche once confirmed.

12.0 APPENDIX

12.1 Appendix 1: List of codes for exclusion of sarcoidosis, allergic alveolitis, pneumoconiosis, asbestosis

Diagnostic Read codes for exclusion of sarcoidosis, allergic alveolitis, pneumoconiosis and asbestosis from Navaratnam *et al.*

Read Code	Read Term_V2	Read Term_V3
AD5..	Sarcoidosis	Sarcoidosis
AD50.	Sarcoidosis of lung	Sarcoidosis of lung
AD51.	Sarcoidosis of lymph nodes	Sarcoidosis of lymph nodes
AD52.	Sarcoidosis of lung with sarcoidosis of lymph nodes	Sarcoidosis of lung with sarcoidosis of lymph nodes
AD53.	Sarcoidosis of skin	Sarcoidosis of skin
AD54.	Sarcoidosis of inferior turbinates	Sarcoidosis of inferior turbinates
AD55.	Sarcoid arthropathy	Sarcoid arthropathy
Cyu06	[X]Sarcoidosis of other and combined sites	[X]Sarcoidosis of other and combined sites
F013.	Meningitis due to sarcoidosis	Meningitis due to sarcoidosis
F3263	Multiple cranial nerve palsies in sarcoidosis	Multiple cranial nerve palsies in sarcoidosis
F3749	Polyneuropathy in sarcoidosis	Polyneuropathy in sarcoidosis
F3965	Myopathy due to sarcoidosis	Myopathy due to sarcoidosis
G5583	Sarcoid heart disease	Sarcoid heart disease
G5y7.	Sarcoid myocarditis	Sarcoid myocarditis
H57y2	Pulmonary sarcoidosis	Pulmonary sarcoidosis
J63A.	Hepatic granulomas in sarcoidosis	Hepatic granulomas in sarcoidosis
N2332	Myositis in sarcoidosis	Myositis in sarcoidosis
Nyu89	[X]Myositis in sarcoidosis classified elsewhere	[X]Myositis in sarcoidosis classified elsewhere
H4...	Lung disease due to external agents	
Xa9Bw		Pneumoconiosis
H40..	Coal workers' pneumoconiosis	Coal workers' pneumoconiosis
H42..	Silica and silicate pneumoconiosis	Silicosis
H420.	Talc pneumoconiosis	Talc pneumoconiosis
H42z.	Silica pneumoconiosis NOS	Silica pneumoconiosis NOS
H43..	Pneumoconiosis due to other inorganic dust	Pneumoconiosis due to other inorganic dust
H43z.	Pneumoconiosis due to inorganic dust NOS	Pneumoconiosis due to inorganic dust NOS
H45..	Pneumoconiosis NOS	Pneumoconiosis NOS
Hyu40	[X]Pneumoconiosis due to other dust containing silica	[X]Pneumoconiosis due to other dust containing silica

Hyu41	[X]Pneumoconiosis due to other specified inorganic dusts	[X]Pneumoconiosis due to other specified inorganic dusts
H41..	Asbestosis	Asbestos pneumoconiosis
H41z.	Asbestosis NOS	Asbestosis NOS
H35..	Extrinsic allergic alveolitis	Extrinsic allergic alveolitis
H35y.	Other allergic alveolitis	Other allergic alveolitis
H35yz	Other allergic alveolitis NOS	Other allergic alveolitis NOS
H35z.	Allergic alveolitis and pneumonitis NOS	Allergic alveolitis and pneumonitis NOS
H35z0	Allergic extrinsic alveolitis NOS	Allergic extrinsic alveolitis NOS
H35zz	Allergic alveolitis and pneumonitis NOS	Allergic alveolitis and pneumonitis NOS

12.2 Appendix 2: List of codes for other causes of pulmonary fibrosis

Read Code	**Read Term_V2**	**Read Term_V3**
X102w	Desquamative interstitial pneumonitis	
X102x	Lymphoid interstitial pneumonitis	
A7899	HIV disease resulting in lymphoid interstitial pneumonitis	
X102y	Giant cell interstitial pneumonitis	
X1030	Toxic diffuse interstitial pulmonary fibrosis	
X1031	Drug-induced diffuse interstitial pulmonary fibrosis	
H4642	Chronic pulmonary fibrosis due to chemical fumes	Chronic pulmonary fibrosis due to chemical fumes
H4y10	Radiation-induced diffuse interstitial pulmonary fibrosis	Chronic pulmonary fibrosis following radiation
X1032	Localised pulmonary fibrosis	
X1033	Mediastinal radiation fibrosis	
X103G	Radiation-induced fibrous mediastinitis	
XE0Ya	Post-inflammatory pulmonary fibrosis	
H55..	Lung: [cirrhosis of] or [postinflammatory pulmonary fibrosis]	
X1046	Pulmonary fibrosis due to sarcoidosis	
C3702	Cystic fibrosis with pulmonary manifestations	

12.3 Appendix 3: Codes for treatment suggestive of IPF

Pirfenidone or Nintedanib

Read Code	Read Term_V2	Read Term_V3	Classification
h8M..	PIRFENIDONE	PIRFENIDONE	Pirfenidone
h8M1.	ESBRIET 267mg capsules	ESBRIET 267mg capsules	Pirfenidone
h8M2.	PIRFENIDONE 267mg capsules	PIRFENIDONE 267mg capsules	Pirfenidone
hhq..	NINTEDANIB	NINTEDANIB	Nintedanib
hhq1.	VARGATEF 100mg capsules	VARGATEF 100mg capsules	Nintedanib
hhq2.	VARGATEF 150mg capsules	VARGATEF 150mg capsules	Nintedanib
hhq3.	NINTEDANIB 100mg capsules	NINTEDANIB 100mg capsules	Nintedanib
hhq4.	NINTEDANIB 150mg capsules	NINTEDANIB 150mg capsules	Nintedanib
hhq5.	OFEV 100mg capsules	OFEV 100mg capsules	Nintedanib
hhq6.	OFEV 150mg capsules	OFEV 150mg capsules	Nintedanib

Free text search term (in clinical table)	Classification
Pirfenidone	Pirfenidone
Esbriet	Pirfenidone
Nintedanib	Nintedanib
Vargatef	Nintedanib
Ofev	Nintedanib

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