

# **IPF JES**


## **Idiopathic Pulmonary Fibrosis Job Exposures Study**

**A case-control study to investigate whether occupational asbestos exposure is an under-recognized cause of idiopathic pulmonary fibrosis (IPF) using an interview to measure previous asbestos exposure and a blood test to investigate genetic susceptibility.**

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**Sponsor**

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This protocol describes the Idiopathic Pulmonary Fibrosis Job Exposures Study (IPF JES) and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator. This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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## Glossary

**Asbestos** Asbestos is a mineral fibre with useful insulating properties. Asbestos use is now strictly controlled because of harmful health effects. Historically, construction materials and household goods have been made from asbestos, and widely used, in the United Kingdom.

**Case-control study** A Case-control study is an observational epidemiological study of persons with a disease of interest and a suitable control group of persons without the disease. The relationship of a suspected risk factor to disease is examined by comparing exposure to the risk factor in the two groups.

**Idiopathic pulmonary fibrosis** Idiopathic pulmonary fibrosis (IPF) is a disease that causes scarring of the lungs. The 'idiopathic' part of the name refers to the cause of the disease being unknown.

## Key words

**Idiopathic pulmonary fibrosis, asbestos, case-control study**

## Study Summary

**Title:** Idiopathic Pulmonary Fibrosis Job Exposures Study (IPF JES).

**Design:** Hospital case-control study.

**Aim:** To characterize and measure asbestos exposure as an occupational determinant of IPF.

**Outcome measures:** 1. Association between asbestos exposure and IPF estimated using conditional logistic regression for any vs no asbestos exposure and categories of cumulative exposure and adjusting for age and smoking status. 2. Gene-environment interaction (for MUC5B rs35705950 and asbestos exposure) odds ratio.

**Population:** Male patients with a new diagnosis of IPF and age-matched controls who have a new outpatient clinic appointment during the study period.

**Eligibility:** Meets population definition, able to give informed consent, has never worked outside of the UK.

**Duration:** Three years.

# 1 Introduction

## 1.1 Background

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrotic lung disease which in 2012 was the recorded cause of death for c.4000 people in England/Wales. Its incidence, currently around 7.5/100,000 person-years, has increased by 5% pa since 2000.<sup>1</sup> The pathophysiology of IPF is complex, the outcome of host susceptibility factors, epithelial injury, and a dysregulated repair process. Several gene polymorphisms which result in a vulnerable alveolar epithelium have been characterized; they include abnormalities in mucin genes (eg MUC5B), surfactant protein genes, and telomerase genes (eg TERT and TERC).<sup>2,3,4</sup> The median age of onset is 70 years and the condition is more common in men (M:F ratio 1.6), manual workers, and those living in industrial areas<sup>1</sup>, patterns that are not unique to the UK.<sup>3</sup> The prognosis is poor, with a median survival of three years.<sup>5,6</sup>

These epidemiological distributions of IPF are consistent with a long-latency response to occupational dust exposure; in particular, the incidence of IPF correlates strongly (if ecologically) with historic asbestos use.<sup>7</sup> Mineralogical studies support the concept of asbestosis-IPF misclassification by revealing high fibre burdens in the lung tissue of patients diagnosed with 'IPF' and revision of the diagnosis to 'asbestosis'.<sup>8,9,10,11</sup>

Identification of occupational asbestos fibre exposure as an under-recognized cause of IPF is important to improve our understanding of the aetio-pathophysiology of IPF and the accuracy of prognostic information. It would have implications for compensation and impact on the current restrictions on individual treatment. Importantly, it would inform evidence-based workplace exposure policies in the UK and internationally, particularly in the many countries with continuing high levels of asbestos use. Details of how the proposed research will inform government policy and change working practices are provided in Appendix A.

In preparing this protocol, I examined mortality trends in England and Wales for IPF and asbestos-related diseases. UK age-standardized mortality rates from 1974 to 2012 continued to rise with marked sex and regional variations, consistent with occupational exposure being an under-recognized cause of IPF.<sup>12</sup> I analysed European age-standardised mortality rates for mesothelioma and IPF for 27 countries for which data was available and found a positive correlation ( $r = 0.51$ ,  $p = 0.007$ ). I collated 13 case-control studies of IPF and occupational dust exposure; eight reported significant associations with metal dust exposure<sup>13,14,15,16,17,18</sup>, four with wood dust<sup>19,20,18,21</sup> and two with stone dust.<sup>22,23</sup>

Finally, I analysed the limited occupational information in a recent case-control study, designed to examine the role of thrombosis in IPF.<sup>1</sup> Using an approach from a large mesothelioma study based on proportional mortality ratios<sup>24</sup> I estimated the odds ratio (OR) associated with ever having had a job with probable asbestos exposure was 2.8 (95% CI: 1.42-5.75,  $p = 0.001$ ) adding further weight to the argument that occupational asbestos exposure in IPF should be properly investigated. Supplementary figures and a table of previous case-control studies are provided in Appendix B.

In addition to its epidemiological and clinical plausibility there are several additional reasons why study of this area is needed. First, most previous work relied on self-reported workplace exposure information, an approach that is open to recall bias and deals poorly with confounding; for example, studies have described strong associations between metal work and IPF and specify sheet metal workers<sup>14,13,16</sup>, a group who are frequently exposed to dust containing asbestos fibres<sup>25</sup> and who in a recent UK study,

had the highest risk of mesothelioma.<sup>24</sup> Lifetime occupational histories are more accurately recalled than self-reported workplace exposures and can be combined with measures such as proportionate mortality (PMR) estimates and job-process assessments to minimize recall bias and more accurately characterise cumulative exposures.<sup>26 27 28 24</sup> This allows too the examination of 'exposure-response' relationships, entirely lacking in the published literature.

Second, all but two studies<sup>14 21</sup> used community controls. While this is generally desirable, hospital controls are preferred in circumstances when acceptable community control participation rates cannot be achieved, case acquisition is incomplete, or recall bias is an issue. Recent participation rates for community controls in UK studies of IPF have been as low as 28%;<sup>29</sup> and a recent US series estimated that the ante-mortem diagnosis of IPF was missed in 20% of cases.<sup>30</sup> Further, the use of community controls for hospital cases risks significant information mismatch on exposures. While hospital controls are less representative of the base population, their use does not prevent a study from being either scientifically valid or generalizable<sup>31</sup> as is well demonstrated by a recent influential UK hospital case-control study which found that exposure to metal fume predisposed to infectious pneumonia.<sup>32</sup>

Third, advances in our understanding of IPF susceptibility now permit study of host-exposure interactions. The minor-allele of the rs35705950 SNP in the mucin 5B gene was found to be present in 38% of IPF patients but just 9% of controls.<sup>33</sup> The polymorphism results in excess MUC5B protein in the airway, impaired clearance of inhaled substances and a chronic inflammatory burden on the alveolar surface.<sup>33</sup> The association is allele dose-dependent, has been replicated in independent cohorts, and appears to confer improved survival.<sup>33 34</sup> Two large GWASs have confirmed the observed associations of IPF with MUC5B and other loci.<sup>35 36</sup>

I propose a new case-control study that systematically collects lifetime occupational histories to derive exposure risk using formal asbestos exposure assessment. I will also collect IPF susceptibility genotypes to permit me, uniquely, to examine exposure-response relationships, latency periods and genotype-exposure interactions.

## 2 Study objectives

My overall aim is to characterize and measure asbestos exposure as an occupational determinant of IPF; additionally, I will determine host-exposure interactions mediated by candidate susceptibility polymorphisms (in particular MUC5B promoter polymorphism rs35705950).

My specific research questions are:

1. Does a dose-response relationship exist for occupational asbestos exposure and IPF?
2. Does the presence of asbestos exposure modify the association between IPF and rs35705950?

## 3 Study design

### 3.1 Study outcome measures

**Primary outcome** Association between asbestos exposure and IPF estimated using conditional logistic regression for any vs no asbestos exposure and categories of cumu-



lative exposure and adjusting for age and smoking status.

**Secondary outcome** Gene-environment interaction odds ratio (for MUC5B rs35705950 and asbestos exposure)

## 4 Participant entry

### 4.1 Pre-registration evaluations

Pre-registration evaluation will include screening for eligibility using inclusion and exclusion criteria.

### 4.2 Sampling

Cases and controls will be frequency matched on age categories.

### 4.3 Inclusion criteria

- Cases
  - Male
  - New diagnosis of IPF between January 2017 and October 2019
- Controls
  - Male
  - New outpatient department attendee between January 2017 and October 2019

### 4.4 Exclusion criteria

- Cases
  - Unable to give informed consent
  - Ever worked outside of the UK
- Controls
  - Unable to give informed consent
  - Ever worked outside of the UK

### 4.5 Withdrawal criteria

Research participants will be withdrawn from the study upon their request or if for any reason they are unable to complete the study interview.

## 5 Adverse events

### 5.1 Definitions

**Adverse Event (AE):** any untoward medical occurrence in a patient or clinical study subject.

**Serious Adverse Event (SAE):** any untoward and unexpected medical occurrence or effect that:

- Is life-threatening refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

### 5.2 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

#### 5.2.1 Non serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to IPF, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Imperial College London where in the opinion of the Chief Investigator, the event was:

- related, ie resulted from the administration of any of the research procedures; and
- unexpected, ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

**Contact details for reporting SAEs:**

Email: carl.reynolds@imperial.ac.uk

Please send SAE forms to:

National Heart and Lung Institute  
Room G39 Emmanuel Kaye Building  
1b Mansrea Road, London, SW3 6LR  
Tel: 07737 904 807

## 6 Assessment and follow up

Research participants will complete an interview and a blood test. The study will end when analysis of the last research participant is complete.

## 7 Statistics and data analysis

For the primary analysis conditional logistic regression will be used to analyse any vs no asbestos exposure and categories of cumulative exposure adjusting for age and smoking status. Prior data indicate that the probability of exposure among controls is 0.63. If the true OR for disease in exposed subjects relative to unexposed subjects is 1.5, I will need to recruit 460 case patients and 460 control patients to be able to reject the null hypothesis that this odds ratio equals 1 with  $\beta = 0.2$  and  $\alpha = 0.05$ ; my planned sample size includes a margin for model stability and incomplete data.

Secondary (exploratory) analysis will investigate gene-environment interaction. The global minor allele frequency of MUC5B rs35705950 is 0.05. With an estimated prevalence of IPF of 20/100000 and with ORs 1.5 for asbestos exposure and 6.8 for rs35705950, 460 cases would be required to detect a minimum interaction OR of 5.0.

## 8 Regulatory issues

### 8.1 Ethics approval

The Chief Investigator has obtained approval from the Research Ethics Committee via IRAS. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

### 8.2 Consent

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. In these cases the participant will be withdrawn from the study and their data and samples destroyed. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

### **8.3 Confidentiality**

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

### **8.4 Indemnity**

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

### **8.5 Sponsor**

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

### **8.6 Funding**

The Wellcome Trust are funding the research.

### **8.7 Audits and inspections**

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

## **9 Study management**

The day-to-day management of the study will be co-ordinated through Dr Carl Reynolds.

## **10 Publication policy**

All research findings will be published in accordance with the Wellcome Trust and Imperial College London open access publication policies.

## Appendix A Research outputs

There will be three main outputs of the study:

1. Data from the study, including anonymised raw data, will be communicated to the wider academic community, and policy-makers, by publication and presentation at national and international respiratory and epidemiology meetings.
2. Data from the study will inform HSE and policy decisions with respect to work place dust control; we are collaborating with Andrew Darnton who works at HSE specialising in mesothelioma and other asbestos related diseases.
3. Data from the study will inform policy decisions with respect to the use of anti-fibrotic treatments in patients with asbestosis. We will establish good working relations with NICE and the NHS England Specialist Respiratory Clinical Reference Group to communicate our findings. NHS patients with IPF due to occult occupational asbestos exposure may be entitled to compensation and our work may lead to reconsideration of current restrictions on disease modifying anti-fibrotic therapies for patients with asbestosis.

An estimated 125 million people around the world work in environments in which they are exposed to asbestos, and at least 107,000 people die from occupational exposure to asbestos every year<sup>37</sup>. Understanding the role of asbestos exposure in idiopathic pulmonary fibrosis is an important data point for disease prevention policy measures.

## Appendix B Supplementary figures and tables



Figure 1: ONS data. Idiopathic Pulmonary Fibrosis, Mesothelioma, and Asbestosis mortality trends for England and Wales 1974-2012. A corrective factor provided by HSE has been applied to pre-ICD 10 Mesothelioma deaths (dashed line). [https://github.com/drcjar/pypf/blob/master/notebooks/pypf\\_analysis.ipynb](https://github.com/drcjar/pypf/blob/master/notebooks/pypf_analysis.ipynb)



Figure 2: ERS Whitebook data. Age standardised mortality rate per 100,000 for 27 European Union member countries (data not available for Greece). Pearson correlation coefficient = 0.51,  $p = 0.007$ . [https://github.com/drcjar/pyypf/blob/master/notebooks/ERS\\_whitebook\\_ipf\\_meso.ipynb](https://github.com/drcjar/pyypf/blob/master/notebooks/ERS_whitebook_ipf_meso.ipynb)

## Summary of case-control studies of occupational dust exposure in IPF by Carl Reynolds

Ref	Country	Cases (N)	Findings	Notes (including source of cases and controls, measure of exposure used, and response rates)
Scott 1990	UK	40	Occupational exposures to metal dust ((OR 10.97, 95%CI 2.3-52.4, p<0.001), wood dust (OR 2.94, 95%CI 0.87-9.9), p = 0.08), and stone/sand (OR 1.59, 95%CI 0.52-4.79) are associated with IPF	Community controls, questionnaire asking directly about exposures, response rate was 87% for cases and 60% for controls.
Iwai 1994	Japan	1311	The IPF rate more than doubled (p <0.01) among subjects engaged in occupations that exposed them to dust or organic solvents	Cases and controls selected from the "Annals of the Pathology Autopsy Cases in Japan" (APACJ) during a 12-yr period (1974-85). The "longest or last" job (according to Japanese Standard Job Category) was exposure measure.
Iwai 1994	Japan	86	Higher odds ratio was noted among metal production workers and miners compared with healthy and hospital control subjects (1.37 and 1.34, respectively, p < 0.01)	Hospital controls. Questionnaire asking directly about exposures.
Hubbard 1996	UK	218	Occupational exposures to metal dust (OR 1.68, 95% CI 1.07-2.65, p = 0.024), wood dust (OR 1.71, 95% CI 1.01-2.92, p = 0.048), and are associated with CFA	Community controls. 92% of eligible cases and 68% of controls returned completed questionnaires and each case had an average of 2.6 controls. Telephone interviews were completed for 76% of cases and for an average of 2.5 controls per case. Exposure response relations (odds ratio per work year of exposure) were OR 1.11, 95% CI 1.06-1.16, p = 0.001 for metal dust and OR 1.12, 95% CI 1.02-1.24 for wood dust.
Mullen 1998	USA	17	Occupational exposure to any dust (OR 2.37, 95% CI 0.67-8.44), asbestos (OR 6.77, 95% CI 0.57-90.7), and silica (OR 11, 95% CI 1.05-115) was associated with ILD	Cases and controls from community clinic, postal questionnaire. 17 of 35 cases contacted (37.7%) and 94 of 290 controls contacted (32.4%) responded to the questionnaire.
Hubbard 2000	UK	55	Direct relation between duration of exposure and the risk of CFA (OR per 10 years of exposure 1.71, 95%CI 1.09-2.68, p=0.02)	Case and controls selected from death certificates held in pension-fund records of employees working for Rolls-Royce Plc at five UK sites. Lifetime occupational data were obtained from individual employment records held by the company for each employee and, and each job was coded according to whether it involved work with meta. Occupational records were located for 40% of cases and 38% of controls.
Baumgartner 2000	USA	248	Occupational exposure to metal dust (OR = 2.0, 95% CI: 1.0, 4.0), stone cutting/polishing (OR = 3.9, 95% CI: 1.2, 12.7), stone cutting/polishing (OR = 3.9, 95% CI: 1.2, 12.7), and vegetable dust/animal dust (OR = 4.7, 95% CI: 2.1, 10.4) are associated with IPF	Community controls, telephone interview asking directly about exposures, 91% of cases and 81% of controls were interviewed.
Miyake 2005	Japan	102	Occupational exposure to metal dust (OR 9.55, 95%CI 1.68-181.12) is an independent risk factor for IPF	Hospital controls. Questionnaires covered "type of job held for the longest period of time" and exposure to 13 specific occupational agents. A full occupational history was not requested.
Gustafson 2007	Sweden	140	Occupational exposure to birch dust (OR 2.7, 95% CI 1.3-5.65) and hardwood dust (OR 2.7, 95% CI 1.14-6.52) are associated with IPF	Community controls, postal questionnaire which asked directly about occupational exposures e.g "Have you ever been exposed to asbestos?"
Pinheiro 2008	USA	84010	Mortality odds ratios were raised for people working in "Wood buildings and mobile homes" (MOR 5.3, 95% CI 1.2-23.8), "Metal mining"(MOR 2.2, 95% CI 1.1-4.4), and "Fabricated metal products"(MOR 1.7, 95% CI 1.0-3.1)	Cases and controls were identified from 1993 to 2003 mortality data and assigned to either the 'exposed' or the 'unexposed' group on the basis of their industry code.
Garcia-Sancho	Mexico	100	Occupational exposure to dusts, smokes, gases or chemicals was associated with IPF (OR 2.4, 95% CI, 1.4-4.0, p = 0.001)	Community controls. A trained interviewer visited every home and administered a structured questionnaire.
Awadalla 2012	Egypt	201	Occupational exposure to wood dust for men (OR 2.71 (1.01-7.37, 95% CI)) and animal feeds, products, and dust (OR 1.78 (1.01-3.13) 95% CI) and insecticides/pesticides (1.04-72.17, 95% CI) for women.	Case response rate was 91%. Age ( $\pm$ 3 yrs), sex, residence, and smoking status matched hospital controls were selected from patients admitted with respiratory disease other than IPF with a 93% response rate. Occupational questions focused on the type of job held for longest period of time during the subjects work life and years of exposure. Questions about exposure to 11 specific occupational and environmental agents were also asked.
Ekstrom 2014	Sweden	171	Smoking has dose related association with increased risk of severe IPF, occupational exposures increase risk	Used the same study design and dataset as Gustafson 2007



## **Appendix C Study flow chart and Gantt chart**

# IPF Asbestos Exposure Study (IPF AES) Flow Chart

## Cases

Inclusion criteria:

- Male
- New diagnosis of IPF between 01.17 and 10.19

4800 new diagnoses of IPF per year at 25 specialist centres

Estimated 3000 potential cases at 17 participating centres randomised sampling from list of all potential cases

Exclusion criteria:

- Unable to consent
- Worked outside of UK

460 Cases

## Controls

Inclusion criteria:

- Male
- New outpatient clinic attendance between 01.17 and 10.19

1 age and sex matched controls for each case randomised sampling from all incident outpatient attendances occurring in the same month

Exclusion criteria:

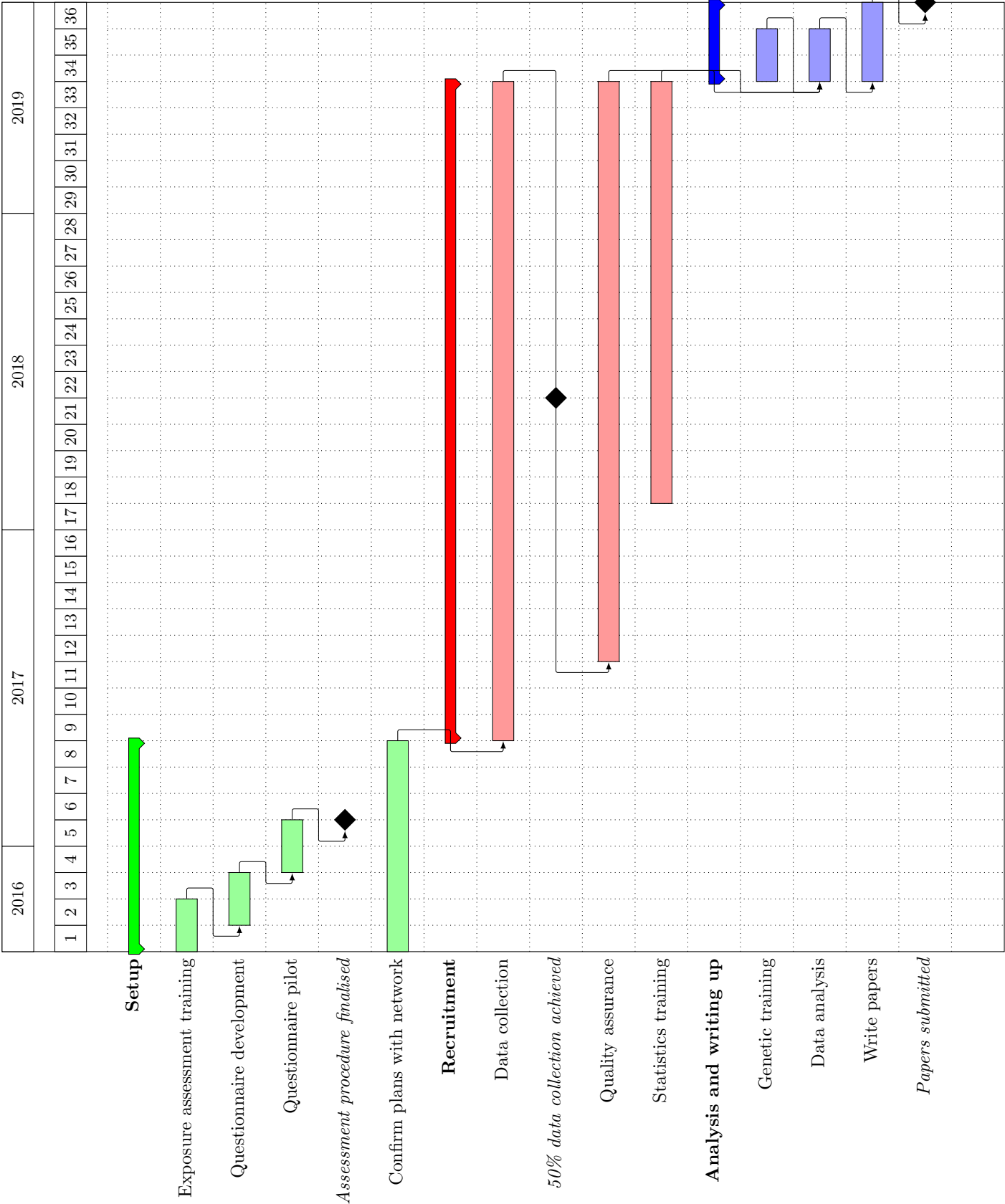
- Unable to consent
- Worked outside of UK
- Diagnosis of IPF

460 Controls

Telephone interview for historic asbestos exposure assessment and blood test for genetic susceptibility

Analysis

IPF Asbestos Exposure Study (IPF JES) 36-Month Gannt Chart



## **Appendix D Study Information Sheet for Health Care Professionals**

## IPF Job Exposures Study (IPF JES)

Previous studies have found associations between occupational metal, stone, and wood dust exposures and IPF but have not looked specifically at quantitative asbestos exposure.

The question of whether job exposures such as asbestos exposure are important in causing a proportion of cases of IPF arises because:

- classical asbestosis looks very like IPF
- the trends of IPF and asbestos use in the UK are closely aligned; while this does not prove causation it is consistent with a link
- it would explain, at least in part, why the disease is more common in men from certain parts of the country
- men who have worked with wood or metals would commonly be exposed also to asbestos
- *preliminary* analysis of occupational data for cases and controls obtained from a recent IPF study shows that the odds ratio associated with ever having had a job where asbestos exposure is likely (using a definition from a large mesothelioma case-control study) is 2.8 (95% CI: 1.42-5.75,  $p = 0.001$ )

Knowing whether there is a link between job exposures such as asbestos and some cases of IPF would help to better understand the causes of IPF; would change approaches to its current treatment; would have important implications for compensation; and would help to prevent the disease in parts of the world where asbestos is still used widely.

We will be recruiting male patients with a new IPF diagnosis (consistent with 2011 ATS/ERS criteria) made between 1/01/2017 and 1/10/2019.

**Study details** This study will recruit men with new diagnoses of IPF (cases) from a network of UK hospitals. For purposes of comparison a group of men of the same age attending the same hospitals at about the same time for other conditions (controls) will be recruited, in a ratio of 1:1; the total number of participants will be 920.

Cases and controls will be invited to give details, through a telephone interview, of all the jobs they have had since leaving school. These jobs will be scored for the likelihood of their incurring exposure to asbestos; the techniques for doing this are well established. The proportions of so-exposed jobs will be compared between the cases and the controls to investigate whether there is a dose-response relationship for occupational asbestos exposure and IPF.

Participants will also be invited to provide a blood sample to investigate whether asbestos exposure modifies the association between idiopathic pulmonary fibrosis and a MUC5B promoter (rs35705950) polymorphism which is known to confer susceptibility to IPF.

**Contact** Dr Carl Reynolds / [carl.reynolds@imperial.ac.uk](mailto:carl.reynolds@imperial.ac.uk) / 07737 904 807  
National Heart and Lung Institute, Room G39 Emmanuel Kaye Building, 1b Manresa Road, London, SW3 6LR.

## **Appendix E Participant Information Sheet**

## Participant Information Sheet

### Idiopathic Pulmonary Fibrosis Job Exposure Study (IPF JES)

**A case-control study to investigate whether job exposures are an under-recognized cause of idiopathic pulmonary fibrosis (IPF) using an interview to collect information about previous jobs and a blood test to investigate genetic susceptibility.**

## PART 1

### Can you help with a research study?

- We would like to invite you to take part in a research study. Before you decide we would like you to understand why the research is being carried out and what it would involve for you.
- One of our team will go through this information sheet with you and answer any questions you have. This should take about 10–15 minutes.
- Please talk to others about the study if you wish and ask us if anything is not clear.

### What is the purpose of the study?

- Idiopathic pulmonary fibrosis (also called IPF) is a disease that causes scarring of the lungs. The scarring damages the air sacs that allow oxygen to be transferred to the blood and transported to vital organs. IPF is a serious illness that causes cough, shortness of breath, and fatigue.
- We don't know what causes IPF but it is becoming more common in England, Scotland and Wales where it affects over 4000 people each year. People who get IPF are usually older than 40; the disease is more common in men and in parts of the country with a history of heavy industry.
- This study will help to find out how much IPF can be attributed to job exposures in England, Scotland and Wales. This will help us to better understand the causes of IPF, make sure people get the right treatment and compensation they are entitled to, and ensure that the controls at work are right so that we protect workers and prevent disease in the future.



### Why have I been chosen?

- The study works by comparing people with IPF (cases) to people who are similar but do not have IPF (controls). Both groups are essential for the study.
- You have been chosen to take part in the study as a **case** if you have a new diagnosis of IPF.
- You have been chosen to take part in the study as a **control** if you do not have IPF but recently had a hospital outpatient appointment and are of a similar age to patients who are newly diagnosed with IPF.

### Do I have to take part?

- It is up to you to decide if you want to take part in the research. We will describe the study and go through this information booklet with you.
- If you agree to take part we will ask you to read and sign a consent form.
- You are free to withdraw at any time, without giving a reason. This will not affect any of the care you receive.

### Who are the researchers?

The research will be conducted by a team based at Imperial College London, Imperial College Healthcare NHS Hospitals, and Sheffield Foundation Trust NHS Hospitals. The research is funded by the Wellcome Trust. The main investigators are:

- Dr Carl Reynolds, Wellcome Trust Clinical Research Training Fellow, Imperial College London. (Chief Investigator)
- Professor Paul Cullinan, Professor, Honorary consultant physician (respiratory medicine). Occupational and Environmental Medicine, NHLI (Imperial College London), Royal Brompton Hospital, London. Joint appointment; tenured. (Co-Investigator)
- Dr Chris Barber, Consultant physician (respiratory medicine), Royal Hallamshire Hospital, Sheffield. (Co-Investigator)
- Dr Sara De Matteis, Clinical Lecturer, Imperial College London. (Co-Investigator)

## PART 2

### What will happen to you if you take part?

- If you agree to take part the researcher will contact you to arrange a telephone interview at a time that is convenient for you.
- The telephone interview will last no longer than one hour.
- During the interview you will be asked questions about
  - All of the jobs you have had since leaving school; we will also ask you about your parents' jobs



- Where you have lived
  - Your lifetime smoking history
- You will be contacted to arrange a blood test to investigate genetic susceptibility to IPF. If possible the blood test will be taken when you next have blood tests to avoid an extra test. If this is not possible it will be arranged at a time and place that is convenient for you. We will cover any reasonable travel expenses incurred due to participation in the study and agreed in advance.
- We will write to you GP to inform them that you are participating.
- We will tell you what we find. What we find might not contain any helpful information for you. If we find anything we think is important we will always tell your clinical team.

### **Are there any benefits to taking part?**

We cannot promise that the study will help you, but the information we get from this research will help to understand the causes of IPF, make sure people get the right treatment and compensation they are entitled to, and ensure that the controls on chemicals at work are right so that we protect workers and prevent disease in the future.

### **Are there any risks to taking part?**

The greatest risk to you of participation in this study is an inadvertent disclosure of your private identifiable information. To minimize the risk of loss of confidentiality your interview response (and blood sample) will not be labelled with your private identifiable information. Interview response information will be kept encrypted on a computer in a locked office. Blood samples will be stored in a secure facility. You will not be identified in any report or publication of this study or its results.

There is a risk that we will find something that is important to your health. This could be distressing to you. If we find anything that we think could be important to your health we will inform your GP and hospital doctors.

### **What will happen when the research is finished?**

A summary of the results will be available and we will send you a copy if you request it. Data from the study, including anonymised unprocessed data, will be communicated to the wider academic community, and policy-makers, by publication and presentation at national and international respiratory and epidemiology meetings. Summary data will also be shared with the care teams participating in the study.

### **What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak to the researchers. They will do their best to answer your questions. Their contact details are on the last page of this booklet. If you remain unhappy and wish to complain formally you can do this by contacting the Patient Advice and Liaison Service (PALS).

Patient Advice and Liaison Service (PALS)  
Ground floor of the Queen Elizabeth the Queen Mother (QEQM) building,  
St Marys Hospital,  
South Wharf Road,  
London W2 1NY.  
Tel: 020 3312 7777  
Email: pals@imperial.nhs.uk

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Carl Reynolds, contact details below). The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Compliance Office.

### **What will happen to the information we collect?**

The Chief Investigator (Dr Carl Reynolds) will be responsible for ensuring that all the information we collect about you during the study is kept strictly confidential. For us to contact you it will be necessary your care team at the hospital to share your contact details with us. Any medical information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

All the procedures used for handling, processing, storage and destruction of your information will be in compliance with the Data Protection Act 1998. All the information we collect will be encrypted and stored on a password protected computer in a secure building. Blood samples will be analyzed and stored in a secure lab at Imperial College London.

Samples and data will be stored for 10 years after the study is finished. Only members of the research team will have access to the information collected and the ability to link it to you. Anonymised samples and data may be shared with academic units and any pharmaceutical collaborators.

**Thank-you for your interest**

**Please ask if you have questions**

### **Contact**

Dr Carl Reynolds / carl.reynolds@imperial.ac.uk / 07737 904 807  
National Heart and Lung Institute  
Room G39 Emmanuel Kaye Building  
1b Manresa Road, London, SW3 6LR

## **Appendix F Participant consent form**

## INFORMED CONSENT FORM FOR SUBJECTS ABLE TO GIVE CONSENT

### Idiopathic Pulmonary Fibrosis Job Exposure Study (IPF JES)

Name of Principle Investigator: \_\_\_\_\_

**Please initial box**

1. I confirm that I have read and understand the subject information sheet dated \_\_\_\_\_ version \_\_\_\_\_ for the above study and have had the opportunity to ask questions which have been answered fully. ☐
2. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from Imperial College London or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to access my records that are relevant to this research. ☐
4. I consent to being contacted by the research team. ☐
5. I consent to genetic testing as part of the research. ☐
6. I consent to storage of information and blood samples collected from me for future research. ☐
7. I consent to my GP and hospital care teams being informed of my participation in the research and of any clinical significant findings arising from the research. ☐

\_\_\_\_\_  
Name of subject

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Subject's date of birth

\_\_\_\_\_  
Name of person taking consent (if different from Principle Investigator)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Principle Investigator

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

## **Appendix G Hospital specialist cover letter (case recruitment)**

# IPF JOB EXPOSURES STUDY (IPF JES)

Cons  
Speciality  
Hospital  
Town  
Postcode

December 2, 2016

**RE: IPF JES**

Dear Doctor,

We have randomly selected one of your patients (**NAME, number, dob**) as a potential case in IPF JES, a multicentre case-control study to investigate job exposures in IPF. The study involves a short interview to measure historic job exposures and a blood test to investigate susceptibility genetics. I enclose a one-page summary of the study together with the participant information sheet and would be happy to answer any questions you might have. Would you be happy to send a cover letter (attached) and information sheet to the patient? We would then hope to enrol them in the study at their next outpatient appointment.

Yours sincerely

Dr Carl Reynolds, Chief Investigator, on behalf of the IPF JES team

A handwritten signature in black ink, appearing to read 'Reynolds', with a large, sweeping flourish extending from the start of the name.

## **Appendix H Hospital specialist cover letter (control recruitment)**

# IPF JOB EXPOSURES STUDY (IPF JES)

Cons  
Speciality  
Hospital  
Town  
Postcode

December 2, 2016

**RE: IPF JES**

Dear Doctor,

We have randomly selected your clinic on date XX/XX/XXXX as a source of potential controls for IPF JES, a multicentre case-control study to investigate job exposures in IPF. The study involves a short interview to measure historic job exposures and a blood test to investigate susceptibility genetics. I enclose a one-page summary of the study together with the participant information sheet and would be happy to answer any questions you might have. Would you be happy for males attending the clinic aged between X and Y to be approached about the study and provided with an information sheet? We would then hope to enrol them in the study at their next outpatient appointment.

Yours sincerely

Dr Carl Reynolds, Chief Investigator, on behalf of the IPF JES team

A handwritten signature in black ink, appearing to read 'Reynolds', with a large, sweeping flourish above it.



## **Appendix I Participant cover letter**

# CLINICAL HEADER

Title Name  
Address1  
Address2  
Address3  
Postcode

December 2, 2016

**RE: IPF JES**

Dear Title Name,

I am writing to invite you to participate in a study of job exposures in IPF. The study involves an interview to measure historic job exposures and a blood test to investigate susceptibility genetics.

I enclose the participant information sheet. Participation is entirely voluntary and whether or not you decide to participate will not change your clinical care.

You do not need to take any action now. If you are interested in the study then the research team will discuss it with you at your next outpatient appointment.

If you wanted to ask the research team anything they are happy for you to contact them (details below).

**IPF JES Research Team**  
**National Heart and Lung Institute,**  
**Room G39 Emmanuel Kaye Building,**  
**1b Manresa Road, London, SW3 6LR**  
**carl.reynolds@imperial.ac.uk**  
**07737 904 807**

Yours sincerely

Name, Principle Investigator, on behalf of the IPF JES team

TITLE NAME • ADDRESS1 • ADDRESS2 • ADDRESS3 • POSTCODE  
✉ NAME@EMAIL.NHS.UK ☎ +44 (X)XX XXXX XXXX

## **Appendix J GP cover letter**

# IPF JOB EXPOSURES STUDY (IPF JES)

Dr General Practitioner  
The Surgery  
1 General Practice Lane  
Practiveville  
London SW1A 2HQ

December 2, 2016

**RE: Joe Bloggs, 12/3/34, NHS number XXX-XXX-XX**

Dear Doctor,

I am writing to inform you that Mr Bloggs has agreed to participate in IPF JES, a multicentre case-control study to investigate job exposures in IPF.

The study involves an interview to measure historic job exposures and a blood test to investigate susceptibility genetics. I will write to inform you if there are any clinically significant findings for your patient.

I enclose the participant information sheet and would be happy to answer any questions you might have.

Yours sincerely

Dr Carl Reynolds, Chief Investigator, on behalf of the IPF JES team

A handwritten signature in black ink, appearing to read 'Reynolds', with a large, sweeping flourish extending from the end of the name.

## **Appendix K Study standard operating procedure**

# Standard Operating Procedure for case and control recruitment and exposure assessment in the Idiopathic Pulmonary Fibrosis Job Exposure Study (IPF JES)

## Contents

<b>1 Scope and applicability</b>	<b>1</b>
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## 1 Scope and applicability

The purpose of this SOP is to describe the instructions for the enrolment of cases and controls, exposure assessment, and genetic testing in the IPF JES.

## 2 Introduction

The objective of IPF AES is to characterize and measure job exposures as an occupational determinant of Idiopathic Pulmonary Fibrosis (IPF). This will be achieved through a case-control study in which historic job exposures are measured using a validated semi-structured interview. A blood test will also be obtained to investigate interaction between job exposures and IPF genetic susceptibility factors.

## 3 Recruitment

### 3.1 Recruitment of cases

See figure 1

Cases will be recruited from male patients with a new diagnosis of IPF made during the study period within the research network.

Centres within the research network will provide the research team with a list of the hospital numbers for all patients newly diagnosed with IPF in the preceding month, on a monthly basis.

For each centre the research team will randomly select a sample from the provided list on a monthly basis. The size of the sample  $N_{centre}$  will be calculated as follows

$$N_{centre} = tp \times (1/nm)$$

Where  $tp$  = total number of patients on list provided,  $nm$  = number of months in the study period.

The research team will request that centres write to these patients inviting them to participate in the study and enclosing the patient information sheet. Patients will be enrolled into the study at their next outpatient department, blood will be drawn, and a telephone interview will be scheduled. Inclusion and exclusion criteria will be checked as part of enrolment.

Recruitment of cases from a centre stops when (460/number of centres) cases are recruited.

## 3.2 Recruitment of controls

See figure 2

Controls will be recruited from male patients with a new outpatient department attendance at the same hospital cases originate from. One male control, frequency matched on age, will be recruited for each case.

Centres within the research network will provide the research team with a list of the outpatient clinics that take place each month to include details of who the lead clinician is for each clinic, average list size, average new to follow up ratio, and when the clinic runs.

The research team will list each clinic alphabetically and serially assign an integer range equal to the expected number of new patients for each clinic per month. The full integer range will then be randomly shuffled and used to derive a list of clinics from which controls will be recruited sequentially. For example, if a particular TB clinic appeared first on the list then all new male patients attending this clinic within the target age range would be approached to participate as controls. If a control could not be found from the TB clinic then the same would be repeated at the next clinic on the list.

The research team will write to the lead clinician for selected clinics to obtain permission to recruit patients to the study. Potential controls will be invited to participate in the study and provided with a patient information sheet when they attend the outpatient department. Patients will be enrolled into the study at their next outpatient department attendance, blood will be drawn, and a telephone interview will be scheduled. Inclusion and exclusion criteria will be checked as part of enrolment.

Recruitment of controls from a centre stops when recruitment of cases stops and one control for each case has been recruited.

## 4 Exposure assessment

### 4.1 Introduction

Hello, my name is **name of researcher**. I am a doctor/nurse/research assistant calling as part of the IPF Job Exposure Study. Is this **name of participant**?

I would like to ask you some questions about the jobs you have had, where you have lived, and your lifetime smoking history. I would also like to record this call for our research if that's ok with you.

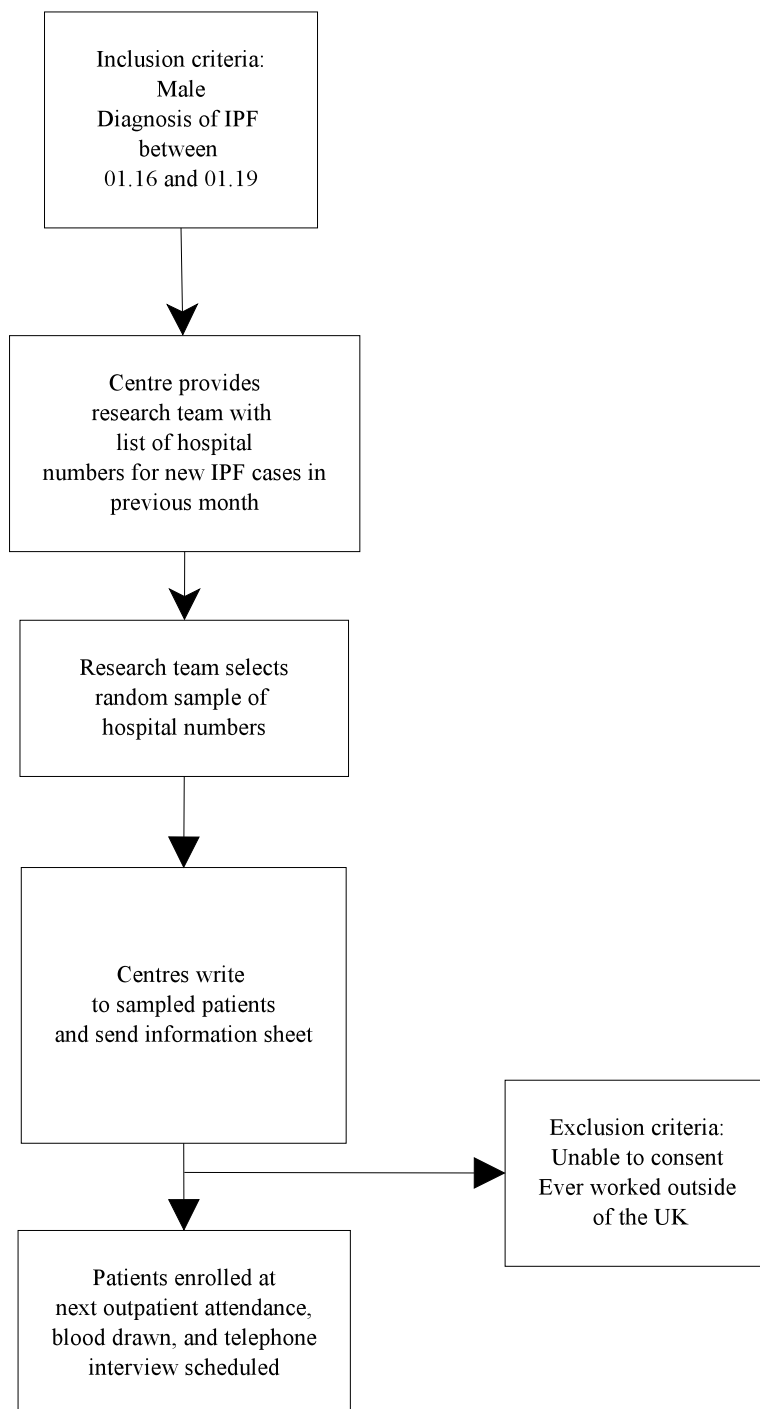


Figure 1: Case recruitment



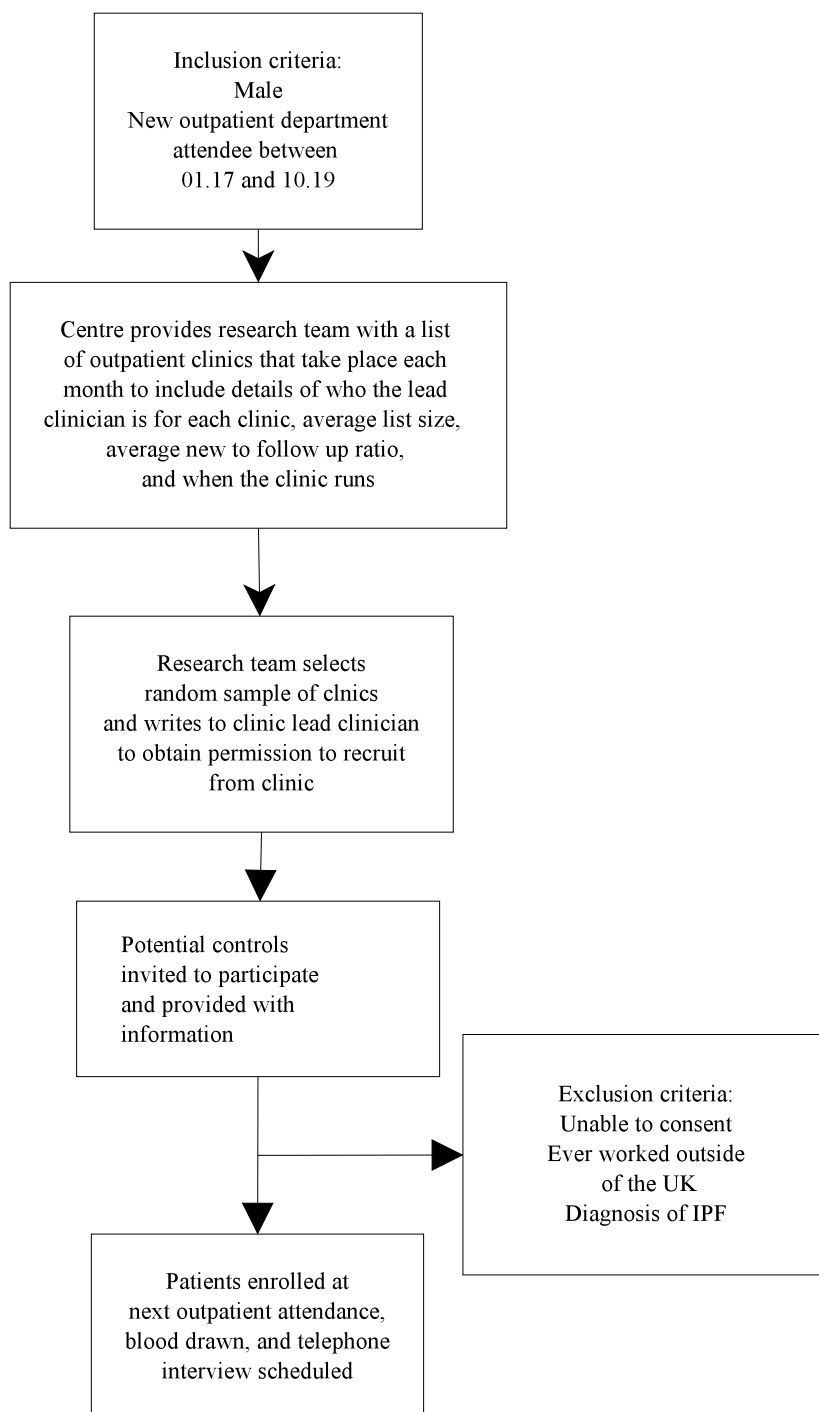


Figure 2: Control recruitment

Your answers will help us to understand the causes of IPF, make sure people get the right treatment, and ensure that controls of exposures at work are right so that we protect workers and prevent disease in the future.

The interview should take about 30 minutes. Is now a good time to talk?

## 4.2 Occupational and residential history

I want you to think about all of the jobs you've had.

Do you remember the first job that you had after school?

1. What was the name of your job?
2. What did you do in this job?
3. What did the company make (if applicable)?
4. Do you remember how old you were or what year you started the job?
5. Do you remember how old you were or what year you finished the job?
6. Do you remember where you lived when you had that job?
7. Do you remember what job you had next?

(1 through 7 repeats until lifetime occupational history is complete. Standard occupational classification is used to code occupations)

'Trigger' jobs prompt more detailed questioning regarding job process(es), materials used, and control measures (according to validated semi-structured job process based historic job exposure assessment tool developed by John Cherrie)

8. What country were you born in?
9. What place were you born in?
10. Do you remember the places you lived when you were growing up? (until you finished school)
11. When you were growing up who lived at home with you?
12. How long for?
13. Do you remember what their job was?

## 4.3 Smoking history

1. Have you ever smoked?
2. What old were you when you started smoking?
3. Do you still smoke?
4. How old were you, or when, did you stop smoking?
5. How many, on average, a day do you/did you smoke?
6. What do you/did you smoke?

#### **4.4 mMRC dyspnoea questions**

I would like to ask you some questions about being short of breath.

Are you:

1. Not troubled by breathless except on strenuous exercise?
2. Short of breath when hurrying on a level or when walking up a slight hill?

Are you someone who:

3. Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace?
4. Stops for breath after walking about 100 yds or after a few minutes on level ground?

Are you:

5. Too breathless to leave the house, or breathless when dressing/undressing?

#### **4.5 (for cases only) how were you diagnosed**

1. What took you to the doctor at the beginning of the illness?

### **5 Venepuncture, sample storage, transportation, and processing**

Venepuncture will be performed by a qualified practitioner. The number of blood tubes to be drawn depends on the volume of the tubes used. A total of 14mls of blood will be obtained using purple top EDTA containers and a total of 10mls of blood using gold top SST tubes for each participant. Samples will be labelled with the participants unique research ID and posted using Royal Mail Safebox to a secure lab storage facility at NHLI where they will be kept in a -80 degree centigrade freezer. The sender will record the day of delivery and the research team will record receipt of the sample and keep an accurate record of its location. Analysis of samples will include DNA isolation and quantitative PCR taqman assay to investigate pre-defined SNPs of interest.

## References

- 1 V Navaratnam, KM Fleming, J West, CJP Smith, RG Jenkins, A Fogarty, and RB Hubbard. The rising incidence of idiopathic pulmonary fibrosis in the uk. *Thorax*, 66(6):462–467, 2011.
- 2 Toby M Maher. Idiopathic pulmonary fibrosis: pathobiology of novel approaches to treatment. *Clin. Chest Med.*, 33(1):69–83, Mar 2012. doi: 10.1016/j.ccm.2011.11.002. URL <http://dx.doi.org/10.1016/j.ccm.2011.11.002>.
- 3 Brett Ley and Harold R Collard. Epidemiology of idiopathic pulmonary fibrosis. *Clinical epidemiology*, 5:483, 2013.
- 4 Paolo Spagnolo, Johan Grunewald, and Roland M du Bois. Genetic determinants of pulmonary fibrosis: evolving concepts. *The Lancet Respiratory Medicine*, 2(5):416–428, 2014.
- 5 Richard Hubbard, Ian Johnston, and John Britton. Survival in patients with cryptogenic fibrosing alveolitis a population-based cohort study. *CHEST Journal*, 113(2):396–400, 1998.
- 6 C. Vancheri, M. Failla, N. Crimi, and G. Raghu. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. *Eur. Respir. J.*, 35(3):496–504, Mar 2010. doi: 10.1183/09031936.00077309. URL <http://dx.doi.org/10.1183/09031936.00077309>.
- 7 CM Barber, RE Wiggans, C Young, and D Fishwick. Uk asbestos imports and mortality due to idiopathic pulmonary fibrosis. *Occup. Med.*, page kqv142, 2015.
- 8 E. Monso, J. M. Tura, M. Marsal, F. Morell, J. Pujadas, and J. Morera. Mineralogical microanalysis of idiopathic pulmonary fibrosis. *Arch. Environ. Health*, 45(3):185–188, 1990. doi: 10.1080/00039896.1990.9936714. URL <http://dx.doi.org/10.1080/00039896.1990.9936714>.
- 9 E Monsó, JM Tura, J Pujadas, F Morell, J Ruiz, and J Morera. Lung dust content in idiopathic pulmonary fibrosis: a study with scanning electron microscopy and energy dispersive x ray analysis. *Br. J. Ind. Med.*, 48(5):327–331, 1991.
- 10 CS Glazer and L Maier. Occupational interstitial lung disease. *Eur Respir Monograph*, 46:265–286, 2009.
- 11 Andrew Ghio, Rahul Sangani, and Victor Roggli. Expanding the spectrum of particle-and fiber-associated interstitial lung diseases. *Turk Toraks Derg*, 15:1–8, 2014.
- 12 C Reynolds, C Barber, and P Cullinan. S3 idiopathic pulmonary fibrosis, mesothelioma, and asbestosis mortality trends for england and wales: Is asbestos exposure associated with ipf? *Thorax*, 69(Suppl 2):A4–A5, 2014.
- 13 Jonathan Scott, Ian Johnston, and John Britton. What causes cryptogenic fibrosing alveolitis? a case-control study of environmental exposure to dust. *BMJ*, 301(6759):1015, 1990.

- 14 K. Iwai, T. Mori, N. Yamada, M. Yamaguchi, and Y. Hosoda. Idiopathic pulmonary fibrosis. epidemiologic approaches to occupational exposure. *Am. J. Respir. Crit. Care Med.*, 150(3):670–675, Sep 1994. doi: 10.1164/ajrccm.150.3.8087336. URL <http://dx.doi.org/10.1164/ajrccm.150.3.8087336>.
- 15 Richard Hubbard, Ian Johnston, David B Coultas, and John Britton. Mortality rates from cryptogenic fibrosing alveolitis in seven countries. *Thorax*, 51(7):711–716, 1996.
- 16 Richard Hubbard, Marie Cooper, Marilyn Antoniak, Andrea Venn, Sayeed Khan, Ian Johnston, Sarah Lewis, and John Britton. Risk of cryptogenic fibrosing alveolitis in metal workers. *The Lancet*, 355(9202):466–467, 2000.
- 17 Yoshihiro Miyake, Satoshi Sasaki, Tetsuji Yokoyama, Kingo Chida, Arata Azuma, Takafumi Suda, Shoji Kudoh, Naomasa Sakamoto, Kazushi Okamoto, Gen Kobashi, et al. Occupational and environmental factors and idiopathic pulmonary fibrosis in japan. *Ann. Occup. Hyg.*, 49(3):259–265, 2005.
- 18 Germania A Pinheiro, Vinicius C Antao, John M Wood, and James T Wassell. Occupational risks for idiopathic pulmonary fibrosis mortality in the united states. *Int. J. Occup. Environ. Health*, 14(2):117–123, 2008.
- 19 R Hubbard, S Lewis, K Richards, J Britton, and I Johnston. Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. *The Lancet*, 347(8997):284–289, 1996.
- 20 Torbjörn Gustafson, Anna Dahlman-Höglund, Kenneth Nilsson, Kerstin Ström, Göran Tornling, and Kjell Torén. Occupational exposure and severe pulmonary fibrosis. *Respir. Med.*, 101(10):2207–2212, 2007.
- 21 N. J. Awadalla, A. Hegazy, R. A. Elmetwally, and I. Wahby. Occupational and environmental risk factors for idiopathic pulmonary fibrosis in egypt: a multicenter case-control study. *Int J Occup Environ Med*, 3(3):107–116, Jul 2012.
- 22 K. B. Baumgartner, J. M. Samet, D. B. Coultas, C. A. Stidley, W. C. Hunt, T. V. Colby, and J. A. Waldron. Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case-control study. collaborating centers. *Am. J. Epidemiol.*, 152(4):307–315, Aug 2000.
- 23 J. Mullen, M. J. Hodgson, C. A. DeGraff, and T. Godar. Case-control study of idiopathic pulmonary fibrosis and environmental exposures. *J. Occup. Environ. Med.*, 40(4):363–367, Apr 1998.
- 24 C. Rake, C. Gilham, J. Hatch, A. Darnton, J. Hodgson, and J. Peto. Occupational, domestic and environmental mesothelioma risks in the british population: a case-control study. *Br. J. Cancer*, 100(7):1175–1183, Apr 2009. doi: 10.1038/sj.bjc.6604879. URL <http://dx.doi.org/10.1038/sj.bjc.6604879>.
- 25 L. S. Welch, D. Michaels, and S. R. Zoloth. The national sheet metal worker asbestos disease screening program: radiologic findings. national sheet metal examination group. *Am. J. Ind. Med.*, 25(5):635–648, May 1994.

- 26 K. Teschke, A. F. Olshan, J. L. Daniels, A. J. De Roos, C. G. Parks, M. Schulz, and T. L. Vaughan. Occupational exposure assessment in case-control studies: opportunities for improvement. *Occup. Environ. Med.*, 59(9):575–93; discussion 594, Sep 2002.
- 27 Eve Bourgkard, Pascal Wild, Maria Gonzalez, Joëlle Févotte, Emmanuelle Penven, and Christophe Paris. Comparison of exposure assessment methods in a lung cancer case-control study: performance of a lifelong task-based questionnaire for asbestos and pshs. *Occup. Environ. Med.*, 70(12):884–891, Dec 2013. doi: 10.1136/oemed-2013-101467. URL <http://dx.doi.org/10.1136/oemed-2013-101467> .
- 28 John W Cherrie and Thomas Schneider. Validation of a new method for structured subjective assessment of past concentrations. *Ann. Occup. Hyg.*, 43(4):235–245, 1999.
- 29 Vidya Navaratnam, Andrew W Fogarty, Tricia McKeever, Norma Thompson, Gisli Jenkins, Simon R Johnson, Gerard Dolan, Maruti Kumaran, Kate Pointon, and Richard B Hubbard. Presence of a prothrombotic state in people with idiopathic pulmonary fibrosis: a population-based case-control study. *Thorax*, 69(3):207–215, Mar 2014. doi: 10.1136/thoraxjnl-2013-203740. URL <http://dx.doi.org/10.1136/thoraxjnl-2013-203740> .
- 30 Craig E Daniels, ES Yi, and Jay H Ryu. Autopsy findings in 42 consecutive patients with idiopathic pulmonary fibrosis. *Eur. Respir. J.*, 32(1):170–174, 2008.
- 31 Kenneth J Rothman, John E J Gallacher, and Elizabeth E Hatch. Why representativeness should be avoided. *Int. J. Epidemiol.*, 42(4):1012–1014, Aug 2013. doi: 10.1093/ije/dys223. URL <http://dx.doi.org/10.1093/ije/dys223> .
- 32 Keith T. Palmer, Jason Poole, Jon G. Ayres, Jonathan Mann, P Sherwood Burge, and David Coggon. Exposure to metal fume and infectious pneumonia. *Am. J. Epidemiol.*, 157(3):227–233, Feb 2003.
- 33 Max A Seibold, Anastasia L Wise, Marcy C Speer, Mark P Steele, Kevin K Brown, James E Loyd, Tasha E Fingerlin, Weiming Zhang, Gunnar Gudmundsson, Steve D Groshong, Christopher M Evans, Stavros Garantziotis, Kenneth B Adler, Burton F Dickey, Roland M du Bois, Ivana V Yang, Aretha Herron, Dolly Kervitsky, Janet L Talbert, Cheryl Markin, Joungjoa Park, Anne L Crews, Susan H Slifer, Scott Auerbach, Michelle G Roy, Jia Lin, Corinne E Hennessy, Marvin I Schwarz, and David A Schwartz. A common muc5b promoter polymorphism and pulmonary fibrosis. *N. Engl. J. Med.*, 364(16):1503–1512, Apr 2011. doi: 10.1056/NEJMoa1013660. URL <http://dx.doi.org/10.1056/NEJMoa1013660> .
- 34 Anna L Peljto, Yingze Zhang, Tasha E Fingerlin, Shwu-Fan Ma, Joe GN Garcia, Thomas J Richards, Lori J Silveira, Kathleen O Lindell, Mark P Steele, James E Loyd, et al. Association between the muc5b promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. *JAMA*, 309(21):2232–2239, 2013.
- 35 Tasha E Fingerlin, Elissa Murphy, Weiming Zhang, Anna L Peljto, Kevin K Brown, Mark P Steele, James E Loyd, Gregory P Cosgrove, David Lynch, Steve Groshong,

- Harold R Collard, Paul J Wolters, Williamson Z Bradford, Karl Kossen, Scott D Seiwert, Roland M du Bois, Christine Kim Garcia, Megan S Devine, Gunnar Gudmundsson, Helgi J Isaksson, Naftali Kaminski, Yingze Zhang, Kevin F Gibson, Lisa H Lancaster, Joy D Cogan, Wendi R Mason, Toby M Maher, Philip L Molyneaux, Athol U Wells, Miriam F Moffatt, Moises Selman, Annie Pardo, Dong Soon Kim, James D Crapo, Barry J Make, Elizabeth A Regan, Dinesha S Walek, Jerry J Daniel, Yoichiro Kamatani, Diana Zelenika, Keith Smith, David McKean, Brent S Pedersen, Janet Talbert, Raven N Kidd, Cheryl R Markin, Kenneth B Beckman, Mark Lathrop, Marvin I Schwarz, and David A Schwartz. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat. Genet.*, 45(6):613–620, Jun 2013. doi: 10.1038/ng.2609. URL <http://dx.doi.org/10.1038/ng.2609> .
- 36 Imre Noth, Yingze Zhang, Shwu-Fan Ma, Carlos Flores, Mathew Barber, Yong Huang, Steven M Broderick, Michael S Wade, Pirro Hysi, Joseph Scuirba, Thomas J Richards, Brenda M Juan-Guardela, Rekha Vij, Meilan K Han, Fernando J Martinez, Karl Kossen, Scott D Seiwert, Jason D Christie, Dan Nicolae, Naftali Kaminski, and Joe G N Garcia. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. *Lancet Respir Med*, 1(4):309–317, Jun 2013. doi: 10.1016/S2213-2600(13)70045-6. URL [http://dx.doi.org/10.1016/S2213-2600\(13\)70045-6](http://dx.doi.org/10.1016/S2213-2600(13)70045-6) .
- 37 M et al Concha-Barrientos. Selected occupational risk factors. In Ezzati M et al, editor, *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors*, volume 2, pages 1651–1802. World Health Organization, 2004. URL <http://www.who.int/publications/cra/chapters/volume2/1651-1802.pdf?ua=1> .