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Applying new technologies in chronic obstructive pulmonary disease (COPD)

Submission date 09/02/2010	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 25/06/2010	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 03/09/2014	**Condition category** Respiratory	[_] Individual participant data

Plain English summary of protocol

Background and study aims
COPD is a very common and debilitating lung disease that can be treated especially in the earlier stages but current diagnosis relies mainly on blowing tests (spirometry) which are not always accurate and can be uncomfortable to do. We want to test new technologies on easy to obtain samples such as sputum (a mixture of saliva and mucus coughed up from the respiratory tract), simpler breath collection and sometimes blood or urine collection. As technology improves, we hope to develop newer ways to diagnose and monitor COPD.

Who can participate?
Patients aged 40 - 90 with a diagnosis of COPD, and healthy individuals with no symptoms of COPD and no evidence of airflow obstruction on spirometry.

What does the study involve?
COPD patients on our hospital database are invited to give breath and sputum samples when well and when suffering an exacerbation; all samples are anonymous. Healthy individuals will be recruited amongst staff, spouses and family members of patients.

What are the possible benefits and risks of participating?
There is no direct benefit for patients and all standard healthcare continues. There are no risks to participants apart from the minor discomfort of a blood test, taken by trained clinicians.

Where is the study run from?
Prince Philip Hospital (UK).

When is the study starting and how long is it expected to run for?
The study will run from January 2010 to December 2015.

Who is funding the study?
Hywel Dda Health Board (UK).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
HD/09/030

Study information

Scientific Title
Testing sputum rheology, sputum fourier transformed infrared spectroscopy and exhaled volatile organic compounds in diagnosing and monitoring chronic obstructive pulmonary disease (COPD)

Acronym
COPD-ANT

Study objectives
Chronic obstructive pulmonary disease (COPD) is the fourth biggest killer in the UK and sufferers are extensive healthcare users. Most people with COPD remain undiagnosed until late in their disease history, yet we now know that early interventions can improve all outcomes. Diagnosis and severity of COPD are currently defined according to breathing tests (spirometry) but these are often unreliable (particularly in the elderly), can be difficult for patients and require specialist interpretation and are not recommended for routine screening. Developing simple, non-invasive and more objective tests for COPD could enable better screening and target resources earlier to make most impact on the disease.

We want to see if new techniques applied to easily obtained samples like sputum and breath can diagnose COPD by detecting novel biomarkers. Certain precise and high throughput technologies have already shown promise in local projects looking at lung cancer.

We hope to recruit 200 patients who have previously attended Hywel Dda Health Board with a range of mild, moderate and severe COPD. Most patients will have their sputum samples and exhaled breath collected whilst in a stable (non-infective) state. Sputum samples will be analysed in Swansea University for mechanical properties (extensional rheology) and chemical bonds using Fourier transform infrared spectroscopy (FTIR) and their breath will be stored and analysed for specific patterns of volatile organic compounds (VOCs).

We also aim to recruit 100 age- and gender-matched controls from spouses, staff and family members (smokers and non-smokers), and patients attending our smoking cessation counselling clinics without symptoms of COPD and normal spirometry. By comparing values between a training set of 80 patients and 50 controls, we hope to develop patterns that will be tested prospectively in the second set of 120 patients and 50 controls. Finally those with COPD who develop 'exacerbations' (sudden worsening of symptoms usually due to chest infection) will also be asked to contact us and if possible, provide breath and sputum samples when becoming unwell to look for any changes in these biomarkers.

On 03/09/2014 the anticipated end date was changed from 31/12/2011 to 08/12/2015.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Dyfed Powys Research Ethics Committee, 17/12/2009, ref: 09/WMW01/34

Study design
Cross-sectional study followed by a longitudinal cohort observational study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Chronic obstructive pulmonary disease (COPD)

Interventions
COPD accounts for 25,000 - 30,000 deaths every year in the UK. COPD prevalence is difficult to estimate because of variable definitions and underdiagnosis. The National Institute of Clinical Excellence (NICE) COPD guidelines (published in 2004) estimated approximately 1.9 million cases in England and Wales. Another survey carried out in 2001 suggested prevalence to be as high as 3.4 - 4.8 million, when defined by lung function tests. Most people in this survey did not have a formal diagnosis of respiratory disease. The Chief Medical Officer for England reported direct healthcare costs for COPD of approximately £800 million every year. Indirect costs of COPD (not including personal morbidity and suffering) are also substantial, amounting to approximately 24 million lost working days per annum.

Lung damage inflicted by smoking and severe COPD is probably irreversible so it is important to identify the disease as early as possible to slow the decline and remove causative agents. However, current guidelines recommend lung function testing only in the presence of symptoms

such as cough, shortness of breath, sputum production and wheeze. This approach tends to miss patients with early disease who would be most suitable for early interventions such as intensive smoking cessation. Mass screening using spirometry has been hampered by uncertainty regarding the most suitable target population, lack of suitably trained personnel and equipment requirements.

Biological markers are being increasingly applied in diagnosing and monitoring of many diseases. New technologies allow cheap and rapid and hence mass throughput of samples, preferably from easy to access and non-invasive samples.

All participants will have the following assessments carried out at baseline:
1. Patient demographics (age, gender)
2. Spirometry
3. Sputum sample collection
4. Exhaled breath collection
5. Exhaled CO level to verify smoking status

Only the COPD patients will have subsequent sputum and breath samples collected in case of an exacerbation (2 years).

Potential participants will be identified by reviewing medical case notes, pulmonary rehabilitation case files and hospital admission records by the direct care team. A Patient Information Sheet (PIS) will be given to all patients and enrolment in the study will occur after obtaining informed consent.

Controls will be recruited amongst staff, spouses and family members of patients after giving them a Control Information Sheet and obtaining consent. General practitioners will be informed after seeking permission from patient participants.

FTIR:
Sputum will be collected from each patient and the FTIR spectra will be obtained using the Bruker Vertex 70 FTIR spectrometer (Bruker Optics Ltd, UK), where samples are spotted on to a 96-well, re-usable silicon sample carrier plate (LNC Technology Ltd., UK). Samples are plated randomly across a plate, permitting possible variations within or between plates to be taken into account during analysis. The loaded sample plates are oven dried at 50°C for 30 minutes in order to remove extraneous moisture prior to FTIR analysis. Prepared plates are allowed to cool and then inserted into the FTIR spectrometer.

Traditional univariate, multivariate statistical (e.g. logistic regression) and data mining methods are to be applied to determine associations between early detection biomarkers, epidemiological factors, disease progression and outcome.

Rheology:
Sputum will be collected from each patient and rheological tests will be conducted using an AR-G2 Controlled Stress Rheometer (TA Instruments, UK) fitted with a low inertia plate-plate (60 mm diameter) measuring system. The system is maintained at the test temperature (either 25°C or 37°C) by means of a peltier temperature control system fitted to a recirculating water bath. In addition, a vapour hood is fitted to minimise any effects due to sample evaporation.

Prior to each rheological test, the requisite volume of sample of sputum/mucus shall be transferred to the rheometer's measuring geometry and the sample will be allowed to equilibrate at the test temperature. Steady flow parameters (e.g. viscosity) will be measured

whilst operating in continuous flow ramp mode. In addition, the viscoelasticity (elastic modulus G' and viscous modulus G'') of the sample will be measured by the application of multiple frequency stress waveforms. These measurements are necessary in order to obtain an extensive rheological characterisation of the samples over a wide range of time scales of deformation.

VOCs:
The patient exhales into the sampler through a disposable mouthpiece until the lungs are as empty as possible. After sample collection, the mouthpiece is removed and replaced with the plunger. A thermal desorption tube containing a suitable sorbent(s) is mounted onto the outlet end of the Bio-VOC sampler. The plunger is pushed in steadily and displaces the trapped air sample onto the thermal desorption tube. The sorbent tube can either be analysed straight away or sealed with long-term storage caps for testing at a later date.

Unity thermal desorption unit (Markes International) is used to desorb the tubes at 280°C for 5 minutes to drive the VOCs onto a cold trap set at -10°C. After the preconcentration step the trap is desorbed at 300°C for 3 minutes and the resultant plug of concentrated sample is injected onto an Agilent Technologies 6890N gas chromatograph (GC) with a 5973 network mass selective detector. The breath VOCs are then separated using capillary column 30 m x 0.25 mm is coated with a film thickness of 0.25 um. The column temperature is initially set at 40°C and then increased to 200°C at a rate of 5°C/min. Mass spectral (MS) data are obtained in the SCAN mode range between 40 - 550 amu. Each GC peak was inspected for constancy of MS pattern and profiles were overlaid for visual qualitative analysis.

Quantitative analysis using chi square, non-paired t-tests/Mann Whitney U and Kaplan Meier survival graphs will be performed following tests for normality on continuous data. The intended outcome is the identification of signature patterns of VOCs that may be associated with COPD, and that may be subsequently applied in a predictive fashion.

University researchers will not know which group the sample came from.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
To develop receiver operator curves for sputum FTIR, sputum extensional rheology and exhaled VOCs in differentiating COPD patients from non-COPD controls. Measured over 2 years.

Key secondary outcome(s))
Measured over 2 years:
1. To correlate changes in sputum FTIR, rheology and exhaled VOCs with severity of airflow obstruction in COPD
2. To compare profiles of sputum FTIR, rheology and exhaled VOCs in stable COPD and during an exacerbation

Completion date
08/12/2015

Eligibility

Key inclusion criteria
1. Patients (aged 40 - 90 years, either sex) with a diagnosis of COPD, according to Global initiative for chronic Obstructive Lung Disease (GOLD)
2. Healthy controls with no symptoms of COPD and no evidence of airflow obstruction on spirometry

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Patients unable or unwilling to give informed consent
2. Those with a current or previous diagnosis of cancer
3. Those with known co-existent asthma, bronchiectasis or pulmonary fibrosis, severe heart failure (ejection fraction [EF] less than 35% on echocardiogram or chronic renal failure - estimated glomerular filtration rate [eGFR] less than 60/ml/min/1.73 m^2)
4. Currently suffering an exacerbation (at enrolment)

Date of first enrolment
01/01/2010

Date of final enrolment
08/12/2015

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Respiratory Department
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Sponsor information

Organisation
Hywel Dda Health Board (UK)

ROR
https://ror.org/012gye839

Funder(s)

Funder type
Government

Funder Name
Hywel Dda Health Board (UK) - paid CRF salary and Research and Development Department Grant covered consumables cost

Funder Name
Other expenses will be met by Dr K E Lewis's (Principal Investigator) research fund.

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	15/02/2013		Yes	No
Results article	results	09/05/2014		Yes	No