establish if factors such as gender, serum ACE level and radiographic stage influence sensitivity thresholds.

Methods Twenty-four patients with sarcoidosis (mean (SEM) age 49 (2) years, 63% female) were recruited from a specialist clinic and underwent assessment of CRS by a single-breath inhalation capsaicin cough challenge test to determine the concentration causing 5 or more coughs (C_5). Anthropometric data, spirometry, serum ACE levels and radiographic stage were recorded. The effects of gender, age, ethnicity, radiographic stage and serum ACE levels on cough reflex sensitivity were investigated. CRS data of 134 healthy subjects from a previous study were used for comparison (Prudon B et al, Chest 2005;127:550).

Results CRS was heightened in patients with sarcoidosis compared to healthy subjects (geometric mean (logSD) C_5 13.5 (0.5) vs 158.5 (0.6) μmol/l, p<0.001). Female patients had a more sensitive cough reflex compared to males (geometric mean (logSD) C_5 8.1 (0.5) vs 31.8 (0.5) μmol/l, p=0.007). Seven patients did not complain of cough; there was no difference in CRS compared to patients who reported cough (p=0.68). There was no difference in CRS between patients of Afro-Caribbean origin compared to non-Afro-Caribbean patients (geometric mean (logSD) C_5 10.1 (0.5) vs 24.3 (0.6) μmol/l, p=0.09). Serum ACE levels correlated significantly with $\log C_5$ (r=0.74, p<0.001), with lower ACE levels being associated with a more sensitive cough reflex. There was no relationship between $\log C_5$ and age (r=−0.40, p=0.054) or radiographic stage (p=0.83).

Conclusions Patients with sarcoidosis have a heightened CRS. This was increased to a greater degree in females, but age or radiographic stage had no effect. We report for the first time a link between serum ACE levels and cough reflex sensitivity, and hypothesise that low concentrations of serum ACE lead to increased airway tussigenic mediators such as bradykinin. Further studies should investigate whether cough receptors such as TRPV1 are upregulated in sarcoidosis.

S137 THE NATURAL HISTORY OF IPF IN PATIENTS ELIGIBLE FOR CLINICAL TRIALS VS PATIENTS NOT ELIGIBLE

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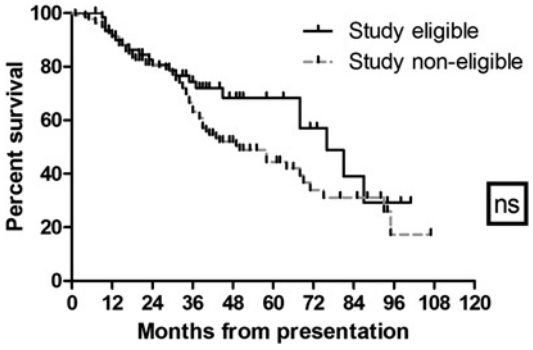
Recruitment to clinical trials is a key objective in the management of IPF. For phase 3 trials, the inclusion and exclusion criteria are stringent. It is not known if the natural history of IPF in patients eligible for clinical trials differs from that in non-eligible patients.

Aims To determine the natural history of IPF in patients eligible for phase 3 trials vs those not eligible

Methods Since 1/1/2002, all patients with IPF presenting to the Edinburgh Royal Infirmary lung fibrosis clinic have been recruited prospectively to a database. The diagnosis of IPF was made by multi-disciplinary consensus after integration of clinical, HRCT and pathological data, based on ATS/ERS criteria. Management and follow-up was by standardised protocol. IPF-directed therapy, including corticosteroids, azathioprine and anti-oxidants, was considered only in advanced disease, acute exacerbation or in those who exhibited pre-specified fall in lung function. Patients were grouped into those eligible for phase 3 clinical trials and those ineligible, based on the major inclusion/exclusion criteria used in a recently published study (CAPACITY, Lancet 2011 377;1760–1769).



Abstract S137 Figure 1 IPF survival.

Results Of 199 consecutively presenting patients with IPF, 61 (31%) were eligible for a phase 3 trial. The proportion of males in the eligible and ineligible groups was similar, but eligible patients were younger (68 vs 74 yrs, p<0.0001), comprised fewer individuals with >20 pack/year smoking history (50% vs 65%, p=0.057), had lower % predicted VC (82.6 vs 95.8 p=0.0003) and higher % predicted TLCO (56.6 vs 51.9, p=0.07). Eligible patients had less % emphysema on HRCT scoring compared to non-eligible patients (0.74% vs 6% p<0.0001). The 3yr-survival of eligible and ineligible patients were not significantly different (Abstract S137 figure 1 74% vs 63%, p=0.3). Event-free survival, defined as time to death *or* =10% fall in VC *or* =15% fall in TLCO *or* acute exacerbation of IPF *or* hospital admission with respiratory illness, was not significantly different between eligible and ineligible groups, such that in both groups 40% and 60% experienced a progression-defining event by 12 -and 24-months respectively.

Conclusions Trial ineligible patients are demographically and phenotypically different from eligible patients, but have identical mortality and progression-free survival. These data have important implications for translation of trial data to clinical practice and for IPF trial design.

S138 TREATING IDIOPATHIC PULMONARY FIBROSIS WITH THE ADDITION OF CO-TRIMOXAZOLE

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Background Idiopathic pulmonary fibrosis is a fatal condition with limited treatment options; however in a previous small study co-trimoxazole has been shown to be beneficial.

Methods In a double-blind, multi-centre study, 181 patients with usual interstitial pneumonia (n=166) or fibrotic non-specific interstitial pneumonia (n=15) were randomised to receive co-trimoxazole 960 mg twice daily or placebo for 12 months in addition to their usual care. Measurements were made of forced vital capacity (FVC), total lung capacity, total lung diffusing capacity of carbon monoxide, Medical Research Council dyspnoea score, St George's Respiratory Questionnaire and quality adjusted life years (QALYs). All cause mortality, costs and adverse events were recorded.

Results Co-trimoxazole had no effect on FVC or other measures of lung function. However in the per-protocol analysis, co-trimoxazole resulted in a significant reduction in mortality (HR of 0.2 (0.06, 0.78)), significant improvements in the symptom domain of St George's Respiratory Questionnaire (mean difference −5.30 (−11.99, 1.40) units) and QALYs gained (mean difference 0.12 (0.01, 0.22) QALYs), and a reduction in the percentage of patients requiring an increase in oxygen therapy (OR 0.05 (0.00, 0.61)) compared to placebo. Furthermore, the use of co-trimoxazole reduced respiratory tract infections. The incremental cost per QALY gained was £21 391 (52.74% probability of being below £30 000; intention to treat analysis, UK societal perspective).

Conclusion The addition of co-trimoxazole therapy to standard treatment for Idiopathic pulmonary fibrosis had no effect on lung function or disease progression but resulted in a fivefold reduction in mortality and was cost-effective at UK thresholds.

Pathophysiology and management of cough

S139 COUGH RESPONSES TO TUSSIVE AGENTS IN HEALTH AND DISEASE

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Introduction Capsaicin or citric acid cough challenges have been used as an objective measure of cough reflex sensitivity for many decades. It remains unclear how the response to these agents differs in different diseases and how the response to one cough challenge agent differs from that to another. Prostaglandin E2 is known to result in cough when given as an inhalational agent, but has not been used as inhalational cough challenge agent.
Objectives To assess the ability of individual challenges and combined challenge responses to discriminate between diagnostic groups and healthy volunteers.
Methods We studied 102 subjects, median age 60.0 years (IQR 51.0–65.0) and 50% female (healthy volunteers n=21, healthy smokers n= 20, COPD n=18, asthma n=22 and chronic cough n=21). A doubling-dose, single inhalation method was used to measure the concentration of capsaicin (CAP), citric acid (CA) and prostaglandin E2 (PGE2) evoking at least 5 coughs (C5) within 15 s of administration, performed at weekly intervals. The operator was blinded to the challenge agent and each challenge contained 3 randomly interspersed placebo inhalations (saline). Data was analysed by multinomial logistic regression with healthy volunteers used as the reference category.
Results Smokers (p=0.03) and COPD patients (p=0.003) had a significantly higher PGE2 logC5 than healthy volunteers. CA logC5 however was significantly lower in asthma (p=0.013), and chronic cough (p=0.001) compared with healthy volunteers. CAP logC5 was also significantly lower in chronic cough (p<0.001) but also in COPD (p=0.035) compared with healthy volunteers. Combining responses to all challenge agents suggested each individual challenge independently predicted the differences between disease groups and healthy volunteers (PGE2 p<0.001, CA p=0.018 and CAP p=0.015).
Conclusions Cough responses to inhalational cough challenges can discriminate healthy controls from airway diseases. Furthermore, cough challenge agents differ in their ability to distinguish health from disease implying different underlying mechanisms drive coughing in these diagnoses. A combination of cough challenge tests appears to be better at discriminating diagnostic groups compared with any individual test in isolation.

S140 PREDICTORS OF 24-H COUGH FREQUENCY IN ACUTE COUGH

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Introduction 24-hour cough frequency monitoring is increasingly being used as an outcome measure to evaluate anti-tussive drugs. The optimal method of identifying patients with a significant cough frequency for inclusion into clinical trials is not known. We investigated a range of cough assessments screening tools that could be used for this purpose.
Methods 35 healthy subjects with acute cough due to upper respiratory infection (median (IQR) age 31 (23–35) years, 63% female, median (IQR) duration of cough 4 (2–6) days) were recruited as part of a larger study. All subjects underwent ambulatory 24-h cough frequency (CF_{24}) monitoring with the Leicester Cough Monitor, health related quality of life with the Leicester Cough Questionnaire-acute (LCQ) and cough severity visual analogue scale (VAS). Receiver operating characteristic curve analyses were performed for the baseline screening tools LCQ, VAS and cough frequency in first hour (CF_1) to identify patients with CF_{24}=5, =7.5 and =10 coughs/hr.
Results The baseline geometric mean (logSD) CF_{24} was 14.7 (0.5) coughs/hr, CF_1 25.9 (0.4) coughs/hr, mean (SEM) VAS 47 (3) mm and LCQ 14.3 (0.7). 4, 6 and 11 patients had CF_{24} <5, <7.5 and <10 coughs/hr respectively. The area under ROC curve (AUC) for VAS and LCQ for prediction of CF_{24} were poor, ranging from 0.51 to 0.58 and 0.50 to 0.68 respectively. The mean (SEM) AUC for CF_1 was 0.92 (0.05), 0.79 (0.10) and 0.86 (0.06) for detecting 24-h cough frequency of =5, =7.5 and =10 coughs/hr respectively. The sensitivity and specificity for cough frequency recordings over 1 h to identify patients with significant 24-h cough frequency are presented in Abstract S140 table 1. A good specificity (to exclude patients with low 24-h cough frequency) was achievable at sensitivities ranging from 69 to 87%.

Abstract S140 Table 1 Accuracy of 1-h cough frequency (CF_1) in identifying 24-h cough frequency (CF_{24})

CF_{24} detection level	Specificity (%)	Sensitivity (%)	CF_1 cut-off level (coughs/hr)	PPV	NPV
>5 coughs/hr	100	87	>12.5	1.00	0.50
>7.5 coughs/hr	83	69	>17.5	0.95	0.36
>10 coughs/hr	92	74	>20.5	0.94	0.65

Conclusion Subjective cough severity and cough-specific quality of life are poor screening tools for predicting objective 24-h cough frequency. However, 1-h cough frequency can be used as a screening tool to identify patients with significant 24-h cough frequency for inclusion into future clinical trials.

S141 TRPA1 EXPRESSION AND CHARACTERISATION IN PATIENTS WITH CHRONIC COUGH

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Introduction and Aims The TRPA1 ion channel is thought to have an important role in the cough reflex. It has been demonstrated that agonisation of TRPA1 receptors by inhalation of cinnamaldehyde, a specific agonist of TRPA1, induces cough in normal human volunteers. We wanted to determine the expression and characterisation of the TRPA1 receptor in human lung tissue.
Methods Bronchial biopsies were obtained from patients with the Cough Hypersensitivity Syndrome on fibre-optic bronchoscopy. Biopsies were obtained from a major bronchus. Lung resection samples were obtained from patients undergoing surgery for lung cancer. Dorsal root ganglia were used as a positive control. These tissue samples were analysed by immunohistochemistry with a specific TRPA1 antibody.