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Treating pulmonary fibrosis with co-trimoxazole

Submission date 28/01/2015	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 29/01/2015	**Overall study status** Completed	
Last Edited 10/12/2020	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims

Pulmonary fibrosis is a rare and poorly understood health condition that is caused by scarring of the lungs. It causes a person to become short of breath when physically active and develop a dry, persistent, cough. It gets worse over time and is often fatal. There is no cure for the condition and treatments given are generally palliative. These include giving patients oxygen though a mask, drug treatments (such as pirfenidone) and, in some cases, a lung transplant may be an option. A previous study has showed that people with pulmonary fibrosis who regularly took an antibiotic (called co-trimoxazole) were 5 times more likely to be alive after one year than those that didn't. However, treatments for pulmonary fibrosis have now changed so researchers now want to see if co-trimoxazole is still as effective. They want to know whether co-trimoxazole, when given alongside current treatments, improves life expectancy and/or reduces the chances of being admitted to hospital for people with pulmonary fibrosis and, by measuring biomarkers (see below), how it may be working.

Who can participate?

Pulmonary fibrosis patients from different regions throughout the UK. All patients must have some degree of breathlessness and reduced breathing tests and not have major health problems, problems with their liver or kidneys.

What does the study involve?

After completing initial assessments and safety blood tests, participants are randomly allocated into one of two groups. Those in group 1 are given co-trimoxazole 960mg twice a day for between 1 year and 3.5 years depending on when they start the study. Those in group 2 are given a placebo tablet for a similar time period. The time until either a participant is admitted to hospital, has a lung transplant or dies is recorded. Questionnaires, breathing tests and blood for biomarkers (chemicals that allow researchers to understand about pulmonary fibrosis) are completed or taken after 3 months, 6 months then every 6 months until the study ends. Patients are also invited to provide a blood sample for genetic testing. Fifty patients are invited to have a bronchoscopy (lung camera test) to find out if co-trimoxazole has an effect on the numbers or amount of inflammatory cells, biomarkers and bacteria (using traditional and new techniques). It is hoped that this study will confirm whether co-trimoxazole has a benefit for patients and, if so, how it may be working.

What are the possible benefits and risks of participating?
Patients may not receive active trial treatment, and may receive the dummy treatment (placebo) but patients will be able to receive any other approved treatment for pulmonary fibrosis from their doctor. Patients may be required to attend the hospital on visits in addition to routine clinic visits for the trial however travel expenses for these will be reimbursed.
Blood tests may cause discomfort and bruising. The questionnaires will take time to complete. The breathing tests may cause slight breathlessness, difficulty breathing or chest discomfort for a few minutes at the most. Patients may experience side-effects listed in the protocol. In addition, its not guaranteed that the study will help patients but the information collected from this study will improve health care professionals ability to treat patients with pulmonary fibrosis in the future.

Where is the study run from?
43 UK NHS hospitals (lead site - Norfolk and Norwich University Hospitals NHS Foundation Trust)

When is the study starting and how long is it expected to run for?
December 2014 to May 2019

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Mr Matt Hammond

Contact information

Type(s)
Scientific

Contact name
Mr Matt Hammond

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Clinical Trials Information System (CTIS)
2014-004058-32

Protocol serial number
18214

Study information

Scientific Title
The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary fibrosis with the Addition of Co-trimoxazole (EME-TIPAC)

Acronym
EME-TIPAC

Study objectives
Pulmonary fibrosis is a condition with limited treatment options. In a previous study we showed that people with pulmonary fibrosis who regularly took an antibiotic (called co-trimoxazole) were 5 times more likely to be alive after one year than those that didn't. However, treatments for pulmonary fibrosis have now changed and we are trying to find out if co-trimoxazole is still as effective. We want to know whether co-trimoxazole, when given alongside current treatments, improves life expectancy and/or reduces the chances of being admitted to hospital for people with pulmonary fibrosis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London - Surrey Borders, 24/11/2014, ref: 14/LO/1800

Study design
Randomised; Interventional; Design type: Not specified, Treatment

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Respiratory disorders; Subtopic: Respiratory (all Subtopics); Disease: Respiratory

Interventions
Co-trimoxazole
Patients will be randomised on a 1:1 basis to receive Oral co-trimoxazole (960mg as 2 tablets of 480mg twice a day) or matched placebo.

Intervention Type
Drug

Drug/device/biological/vaccine name(s)
Co-trimoxazole

Primary outcome(s)
The primary outcome will be the time to death (all causes), lung transplant or the first non-elective hospital admission.

Key secondary outcome(s))
1. Clinical questionnaires
2. Oxygen saturation
3. Lung function
4. Biomarkers
5. Routine microbiology
6. Adverse events
7. FBC, U&E, LFT

Completion date
31/05/2019

Eligibility

Key inclusion criteria
Inclusion criteria as of 21/11/2016:
1. Male or female, aged greater than or equal to 40 years. IPF rarely occurs in individuals less than 40 years. Individuals younger than this more frequently have connective tissue related lung disease which is similar to but different from IPF.
2. A diagnosis of idiopathic pulmonary fibrosis (IPF) based on multi-disciplinary consensus according to the latest international guidelines.
3. Patients may receive oral prednisolone up to a dose of 10 mg per day, anti-oxidant therapy, pirfenidone or other licensed medication for IPF e.g. nintedanib. Patients should be on a stable treatment regimen for at least 4 weeks to ensure baseline values are representative.
4. MRC dyspnoea score of greater than 1.
5. Able to provide informed consent.; Target Gender: Male & Female ; Lower Age Limit 40 years

Original inclusion criteria:
1. Male or female, aged greater than or equal to 40 years. IPF rarely occurs in individuals less than 40 years. Individuals younger than this more frequently have connective tissue related lung disease which is similar to but different from IPF.
2. A diagnosis of idiopathic pulmonary fibrosis (IPF) based on multi-disciplinary consensus according to the latest international guidelines within 2 years of enrollment into the study. Patients with a diagnosis of more than 2 years duration can be enrolled if they have evidence of progressive disease defined as =10% decline in forced vital capacity (FVC) or =15% decline in diffusing capacity of carbon monoxide over the preceding 6 or 12 months.
3. Patients may receive oral prednisolone up to a dose of 10 mg per day, anti-oxidant therapy, pirfenidone or other licensed medication for IPF e.g. nintedanib. Patients should be on a stable treatment regimen for at least 6 weeks to ensure baseline values are representative.
4. MRC dyspnoea score of greater than 1.
5. Able to provide informed consent.; Target Gender: Male & Female ; Lower Age Limit 40 years

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
342

Key exclusion criteria
Exclusion criteria as of 21/11/2016:
1. FVC > 75% predicted.
2. A recognised significant co-existing respiratory disease, defined as a respiratory condition that exhibits a greater clinical effect on respiratory symptoms and disease progression than IPF as determined by the principal investigator.
3. Patients with airways disease defined as forced expiratory volume in 1 second (FEV1) /FVC<60%
4. A self-reported respiratory tract infection within 4 weeks of screening defined as two or more of cough, sputum or breathlessness and requiring antimicrobial therapy.
5. Significant medical, surgical or psychiatric disease that in the opinion of the patient's attending physician would affect subject safety or influence the study outcome including liver (Serum transaminase > 3 x upper limit of normal (ULN), Bilirubin > 2 x ULN) and renal failure (creatinine clearance <30ml/min).
6. Patients receiving recognised immunosuppressant medication (except prednisolone above) including azathioprine and mycophenolate mofetil.
7. Female subjects must be of non-childbearing potential, defined as follows: postmenopausal females who have had at least 12 months of spontaneous amenorrhoea or 6 months of spontaneous amenorrhoea with serum FSH>40mIU/ml or females who have had a hysterectomy or bilateral oophorectomy at least 6 weeks prior to enrolment.
8. Allergy or intolerance to trimethoprim or sulphonamides or their combination.
9. Untreated folate or B12 deficiency.
10. Known glucose-6-phosphate dehydrogenase (G6PD) deficiency or G6PD deficiency measured at screening in males of African, Asian or Mediterranean descent.
11. Receipt of an investigational drug or biological agent within the 4 weeks prior to study entry or 5 times the half-life if longer.
12. Receipt of short course antibiotic therapy for respiratory and other infections within 4 weeks of screening.
13. Patients receiving long term (defined as >1 month of therapy) prophylactic antibiotic treatment will not be eligible as this may have an impact on lung microbiota. Such patients may enrol in the EME-TIPAC trial, if this is supported by their clinician, after a 'wash-out period' of 3 months.
14. Serum Potassium greater than 5.0 mmol/l due to the potentially increased risk of hyperkalaemia in patients taking co-trimoxazole in combination with potassium sparing diuretics (including angiotensin converting enzyme inhibitors or angiotensin receptor blockers)

Original exclusion criteria:
1. FVC > 70% predicted.
2. A recognised significant co-existing respiratory disease, defined as a respiratory condition that exhibits a greater clinical effect on respiratory symptoms and disease progression than IPF as determined by the principal investigator.
3. Patients with airways disease defined as forced expiratory volume in 1 second (FEV1) /FVC<60%
4. A self-reported respiratory tract infection within 4 weeks of screening defined as two or more of cough, sputum or breathlessness and requiring antimicrobial therapy.

5. Significant medical, surgical or psychiatric disease that in the opinion of the patient's attending physician would affect subject safety or influence the study outcome including liver (Serum transaminase > 3 x upper limit of normal (ULN), Bilirubin > 2 x ULN) and renal failure (creatinine clearance <30ml/min).
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11. Receipt of an investigational drug or biological agent within the 4 weeks prior to study entry or 5 times the half-life if longer.

Date of first enrolment
15/05/2015

Date of final enrolment
31/05/2018

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Norfolk and Norwich University Hospitals NHS Foundation Trust (lead site)
Colney Lane
Norwich
United Kingdom
NR4 7UY

Sponsor information

Organisation
Norfolk and Norwich University Hospital NHS Trust

ROR
https://ror.org/01wspv808

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

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	08/12/2020	10/12/2020	Yes	No
Protocol article	protocol	05/02/2018		Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes