The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary Fibrosis with the addition of Co-trimoxazole (EME-TIPAC)

Version	3.0
Date	16th May 2016
Sponsor	Norfolk and Norwich University Hospitals NHS Foundation Trust (NNUH)
EUDRACT	2014-004058-32
ISRCTN	17464641
CTA #	13630/0008/001-0001
REC Reference #	14/LO/1800
Name	Prof Andrew Wilson
Role	Chief Investigator
Signature	
Date	14 JUN 2016
Name	Lisa Chalkley
Role	Sponsor Representative
Signature	
Date	16th June 2016.
Name	Prof Ann Marie Swart
Role	NCTU Director
Signature	
Date	14/6/16.
Name	Dr Allan Clark
Role	Medical Statistician
Signature	
Date	15/6/16

Table of Contents

1 Administrative information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol Template Version 2.0. It describes the Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary Fibrosis with the addition of Co-trimoxazole (EME-TIPAC) trial, which is sponsored by Norfolk and Norwich University Hospital NHS Foundation Trust (NNUH) and co-ordinated by NCTU.

It provides information about procedures for entering patients into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the Protocol Template is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement for protocols of clinical trials[1] and the Elaboration document[2].

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). Agreements that include detailed roles and responsibilities will be in place between participating sites and NCTU.

Participating sites will inform NCTU by phone or email as soon as they are aware of a possible serious breach of compliance, so that NCTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). The Chief Investigator (CI) and NCTU Director will assess whether or not the breach is 'serious'. For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

NNUH is the trial sponsor and has delegated responsibility for the overall management of the EME-TIPAC trial to NCTU including the delivery of the trial to time, target and budget.

1.3 Structured trial summary

Public Title	Treating pulmonary fibrosis with co-trimoxazole
Scientific Title	The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary Fibrosis with the addition of Co-trimoxazole (EME-TIPAC): a randomised controlled trial
Primary Registry and Trial Identifying Number	ISRCTN: 17464641 Eudract: 2014-004058-32
Source of Monetary or Material Support	National Institute for Health Research Efficacy and Mechanism Evaluation Programme Grant number 12/206/09
Sponsor	Norfolk and Norwich University Hospital NHS Foundation Trust
Contact for Public Queries	EME-TIPAC@uea.ac.uk
Contact for Scientific Queries	EME-TIPAC@uea.ac.uk
Countries of Recruitment	UK
Health Condition(s) or Problem(s) Studied	Idiopathic Pulmonary Fibrosis
Intervention(s)	Patients will be randomised on a 1:1 basis to receive, for between 12 and 42 (median 27) months: Active intervention: • Oral co-trimoxazole: 960mg as 2 tablets of 480mg twice a day Control intervention: • Oral placebo: 2 tablets twice a day In addition, all patients will receive 5mg folic acid once a day.
Key Entry Criteria	**Inclusion criteria:** 1) Male or female, aged greater than or equal to 40 years. 2) A diagnosis of Idiopathic Pulmonary Fibrosis (IPF) based on local or regional multi-disciplinary consensus according to the latest international guidelines (Am J Respir Crit Care Med 2011;183(6):788-824) 3) Patients may receive oral prednisolone up to a dose of 10 mg per day, anti-oxidant therapy, Pirfenidone, Nintedanib or other licensed medication for IPF. 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. **Exclusion criteria:** 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 obstructive airways disease defined as forced expiratory volume in 1 second (FEV1)/FVC<60% 4) Patients with 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 will not be eligible because of the difficulty of obtaining reliable baseline lung function 5) Significant medical, surgical or psychiatric disease that in the opinion of the patient's attending physician would affect subject safety including liver (Serum transaminase > 3 x upper limit of normal (ULN), Bilirubin > 2 x ULN (unless Gilbert's Syndrome) and renal failure (creatinine clearance <30ml/min) or significantly impact his/her ability to comply with treatment or follow up. 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 amenorrhea or 6 months of spontaneous amenorrhoea with serum FSH>40mIU/ml or females who have had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy at least 6 weeks prior to enrolment. 8) Known 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 drug half-life, whichever is the 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
Study Type	The study is a Phase III double blind, parallel group, randomised placebo controlled multi-centre clinical trial of oral co-trimoxazole versus placebo in 330 patients with moderate and severe Idiopathic Pulmonary Fibrosis. Randomisation will be performed centrally according to a computer-generated randomisation code with secure e-mail correspondence by Norwich CTU to research pharmacists only. There will be minimisation for: research site, whether patients undergo a baseline bronchoscopy, whether patients are receiving baseline licensed medication for IPF.
Date of First Enrolment	15th May 2015
Target Sample Size	330

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 Outcomes	The individual components of the primary outcome: time to death (all causes), lung transplant and first non-elective hospital admission, will be analysed separately as secondary outcomes. Additionally, the following measurements will be undertaken at baseline, at 3 and 6 months after randomisation, then 6 monthly and at end of study/hospitalisation: • (i) the King's Brief Interstitial Lung Disease (K-BILD) health related quality of life questionnaire; (ii) the MRC Breathlessness Score; (iii) the EQ5D quality adjusted life year's assessment; (iv) cough visual analogue score; (v) global rating of concept scale. • Oxygen saturation • Lung function including spirometry and total lung diffusing capacity of carbon monoxide (DLCO) • Routine microbiology on sputum and nasal swabs At baseline and at 12 months the following will be measured: • Leicester cough questionnaire • Global rating of change Safety outcomes (0, 6 weeks, 3, 6, 9, 12 months, then 6 monthly and end of study): • Adverse events • Full blood count and differential white cell count • Urea and electrolytes • Liver function In addition, blood will be taken (0, 3 months, 6 months, 12 months and end of study/hospitalisation) and stored for analysis of biomarkers In a subset of 50 patients who agree to bronchoscopy, bronchoalveolar lavage fluid (BALF) will be obtained at 0 and 3 months (and if clinically indicated at a hospitalisation) for: • Molecular analysis including but not limited to high throughput sequencing of DNA derived from bacterial 16S ribosomal RNA genes • Differential cell count • Quantitative microbiology culture • Pneumocystis jirovecii identification by polymerase chain reaction (PCR) • Alveolar epithelial cell injury markers • Neutrophil function markers • Collagen turnover markers

1.4 Time and Events table

	Enrolment	Randomisation	Post-allocation[1]						Close-out
TIMEPOINT	*-28 to -1 days*	*0*	*6 weeks*[2]	*3 months*	*6 months*	*9 months*[2]	*12 months*	*every 6 months.*	*End of study or first non-elective admission*
Informed consent	X								
Demographics etc	X								
Entry criteria	X								
Allocation		X							
Investigational Medicinal Product dispensed		X		X	X		X	X	
Safety bloods[3] (FBC, U&Es, LFTs)	X		X	X	X	X	X	X	X
B12, Folate, G6P4[4]	X								
DNA	X								
Biomarkers	X			X	X		X		X
K-BILD, MRC Breathlessness Score, EQ5D, Cough Score, Global Rating of Concept Scale	X			X	X		X	X	X
Leicester Cough Questionnaire, Global Rating of Change – QOL	X						X		
Full lung function	X			X	X		X	X	X
Microbiology (as clinically indicated)	X		X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X
BALF (subgroup) [5]	X			X					X

1 Visits within the first 6 months should be within ±2 weeks, after 6 months visits should be within ±1 month of the schedule. Where possible, visits should be arranged prior to the time-point to ensure patients have sufficient supply of IMP available.

2 Unless the patient is otherwise due to attend a clinic visit at the 6 week and 9 month time-points as part of their standard care, the safety bloods for these visits can be performed at the patients GP surgery and the patient followed up via telephone (to check for adverse events and any change in concomitant medication).

3 Patients over 66 years old, with an initial Potassium between 4.7 and 5.0 mmol/L who are taking potassium sparing diuretics (including angiotensin converting enzyme inhibitors or angiotensin receptor blockers) are required to have an extra safety blood test 1 week after starting treatment (see Section 6.4.5 for more information)

4 G6P is only required for patients of African, Asian or Mediterranean descent.

5 BALF only performed by selected centres. 3 month BALF can be performed from 10 to 17 weeks after treatment

NB: Shaded cells are normally part of routine clinical care

1.5 Roles and responsibilities

1.5.1 Role of trial sponsor, those with major delegated activities and funders

Name	Role
Norfolk and Norwich University Hospital NHS Foundation Trust	Sponsor – overall responsibility for the conduct of the study
NIHR EME	Funder – responsibility for trial design and funding
Norwich CTU	Responsibility for design, data collection, analysis and dissemination within budget.

1.5.2 Trial Team

Name	Affiliation	Role and responsibilities
Professor Andrew Wilson	University of East Anglia	Chief Investigator
Matthew Hammond	NCTU	Clinical Trial Manager
Megan Jones	NCTU	Clinical Trial Assistant
Dr Allan Clark	University of East Anglia	Statistician
Sue Stirling	University of East Anglia	Statistician
Martin Pond	NCTU	Head of Data Management
Professor Ann Marie Swart	University of East Anglia	Co-investigator

1.5.3 Trial Management Group

Name	Affiliation	Role and responsibilities
Professor Andrew Wilson	University of East Anglia	Chief Investigator
Matthew Hammond	NCTU	Clinical Trial Manager
Dr Allan Clark	University of East Anglia	Statistician
Martin Pond	NCTU	Head of Data Management
Dr Tony Cahn	Bedford Hospitals NHS Trust	Co-investigator
Dr Helen Parfrey	Papworth Hospital NHS Foundation Trust	Co-investigator
Dr David Thickett	University of Birmingham	Co-investigator
Prof Moira Whyte	University of Edinburgh	Co-investigator
Dr Toby Maher	Royal Brompton & Harefield NHS Foundation Trust	Co-investigator
Professor Bill Fraser	University of East Anglia	Co-investigator
Professor David Livermore	University of East Anglia	Co-investigator
Professor Ann Marie Swart	University of East Anglia	Co-investigator
In addition a Patient Representative will be invited to attend trial management group meetings		

1.5.4 Trial Steering Committee

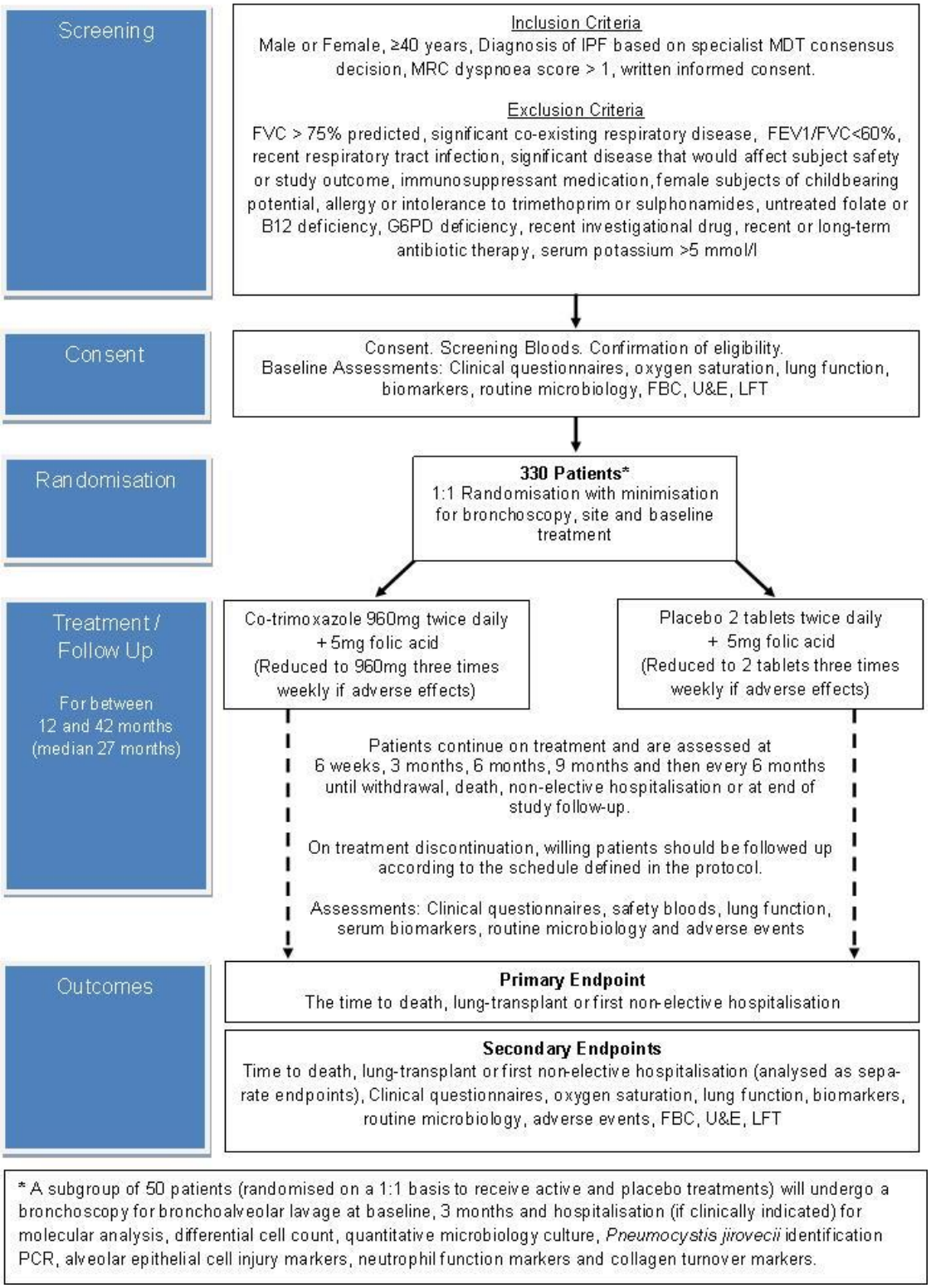
Name	Affiliation	Role and responsibilities
Prof Ron du Bois	Imperial College	Independent Chair
Dr Nicholas Harrison	University of Swansea	Independent Member
Professor Ann Millar	University of Bristol	Independent Member
Dr Sanjay Agrawal	University Hospitals Leicester NHS Trust	Non-Independent Member
In addition a Patient Representative will be invited to attend committee meetings		

1.5.5 Data Monitoring Committee (independent members)

Name	Affiliation	Role and responsibilities
Dr Nik Hirani	University of Edinburgh	Chair
Dr Jack Bowden	MRC Biostatistics Unit, Cambridge	Statistician
Dr Sarah Pett	MRC Clinical Trials Unit, UCL	Member

2. Trial Diagram

The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary Fibrosis with the addition of Co-trimoxazole (EME-TIPAC)



3 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
BALF	Bronchoalveolar lavage fluid
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRP	C-Reactive Protein
CTA	Clinical Trial Authorisation
DLCO	Diffusing capacity of the lung for carbon monoxide
DSUR	Development Safety Update Report
EME	Efficacy and Mechanism Evaluation
EQ5D	Euroqol 5-dimension questionnaire
EU	European Union
FEV1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HRCT	High resolution computed tomography
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IIP	Idiopathic Interstitial Pneumonia
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ITT	Intention to Treat
ISRCTN	International Standard Randomised Controlled Trial Number
K-BILD	King's Brief Interstitial Lung Disease
MDT	Multi-disciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
MMP	Matrix Metalloproteinase
MoU	Memorandum of Understanding
MRC	Medical Research Council
NCTU	Norwich Clinical Trials Unit
NICE	National Institute for Health and Clinical Excellence
NNUH	Norwich and Norfolk University Hospitals NHS Foundation Trust
PI	Principal Investigator
PIS	Participant Information Sheet
PJ	*Pneumocystis jirovecii*
PP	Per Protocol
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QC	Quality Control
R&D	Research and Development
REC	Research Ethics Committee
RNA	Ribonucelic Acid
RGF	Research Governance Framework
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SP	Surfactant Proteins
SPC	Summary of Product Characteristics
SSA	Site Specific Approval
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLR	Toll-like receptor
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UEA	University of East Anglia
UIP	Usual Interstitial Pneumonia

4 Introduction

4.1 Background and Rationale

4.1.1 Idiopathic Pulmonary Fibrosis: a condition with great unmet need.

Idiopathic Pulmonary Fibrosis (IPF) is a progressive and usually fatal lung disease with a 5 year survival of 20-40%[3]. At 7.44 per 100,000 person years[4], the incidence of IPF is similar to subarachnoid haemorrhage[5], ovarian cancer and myeloma (5th and 6th commonest UK cancers)(cancerresearchuk.org). More people will die each year from IPF than from ovarian cancer, leukaemia or mesothelioma[4]. Current therapies are of limited efficacy, with only oxygen and lung transplantation recommended by international guidelines[6]. Immunosuppressive therapy is no longer advised[7] and initial beneficial effects of N-acetyl cysteine[8] have not be substantiated when given as monotherapy[9]. Warfarin reduced mortality in an open-labelled study but not in a placebo-controlled trial[10]. Pirfenidone[11 12] and BIBF-1120[13 14] reduce the rate of decline in lung function. Shulgina et al investigated the role of co-trimoxazole in patients with IPF in Treating Idiopathic Pneumonitis with the Addition of Co-trimoxazole (TIPAC)[15] and found a 5-fold reduction in mortality in patients adhering to treatment. This finding requires further evaluation, along with exploration of the mechanism of action to target better the therapy and aid the development of new therapies.

4.1.2 Potential beneficial effect of co-trimoxazole.

A literature review of clinical trials of co-trimoxazole therapy in the management of IPF has been undertaken using the MedLine database and the search terms [“idiopathic pulmonary fibrosis” or “cryptogenic fibrosing alveolitis” or “Usual Interstitial pneumonitis” or “IPF” or “CFA” or “UIP”] and [“co-trimoxazole” or “trimethoprim” or “sulphamethoxazole”]. The search revealed only two placebo-controlled studies [15][16]. In one study of 20 patients, 3 months co-trimoxazole 960mg twice daily improved the primary endpoint of shuttle walk distance as well as forced vital capacity (FVC) and Medical Research Council (MRC) dyspnoea score[16].

In TIPAC[15], the effect of co-trimoxazole 960mg twice daily for 12 months was evaluated in 181 patients with Idiopathic Interstitial Pneumonia (IIP), 166 of whom had classical IPF. Although there was no effect on FVC (primary endpoint) or other lung function measurements, co-trimoxazole was cost-effective in the intention to treat (ITT) analysis from the NHS perspective in terms of incremental cost per quality of life years (QALYs) gained. In a per protocol (PP) analysis, the co-trimoxazole treated group demonstrated significant reductions in mortality compared to placebo (3/53 versus 14/65, odds ratio 0.21 95% CI 0.06 to 0.78), had improvements in QALYs and reduced need for oxygen therapy. The findings were similar when confined to classical IPF and were not influenced by baseline immunosuppressive therapy. The results were even more striking when considering patients with impaired lung function. Patients with an FVC ≤ 75 percent of predicted normal (% predicted) were nearly twice as likely to be admitted to hospital or die than patients with an FVC > 75% predicted, with a borderline significant (p=0.053) treatment effect in this subgroup using these combined endpoints (post hoc sensitivity analysis on ITT basis from TIPAC).

4.1.3 Aetiology of IPF and potential mechanisms of co-trimoxazole

As the pathogenesis of IPF is unknown the potential mechanisms of action of co-trimoxazole are uncertain. Co-trimoxazole is a broad spectrum antibiotic with bactericidal effects against respiratory

pathogens and the role of infection in IPF is becoming more evident. However, it may have non-antimicrobial effects, targeting cellular processes which have been implicated in the pathogenesis of IPF.

4.1.3.1 Anti-microbial effects

The role of infection in the pathogenesis of IPF has not been fully evaluated[6]. Infection is common in patients with IPF - even those not receiving immunosuppression. In TIPAC[12], 62% of the patients in the placebo group not receiving prednisolone had an infection during the study period[17]. In a meta-analysis of patients allocated to placebo from clinical trials of patients with IPF, reported rates of pneumonia were 37.1 per 1000 patient years in studies not permitting immunosuppression[18] which is even higher than in COPD[19]. Mortality from IPF is increased in winter even when recognised infection is excluded[20].

More than 1/3rd of patients with IPF are colonised with pathogenic bacteria[21] or *Pneumocystis jirovecii*[22], the majority of which are sensitive to co-trimoxazole. More recently researchers have evaluated the lung microbiota by sequencing of bacterial 16S ribosomal RNA genes and shown that the lung of patients with interstitial lung disease is not sterile[23]. Two independent groups of researchers using 16s technology have shown that bacterial load[24] and the lung microbiota profile enriched with Streptococcus and Staphylococcus[25] predict poor outcome in IPF. The stability of the lung microbiota, and the response to antibiotic therapy, are unknown in IPF.

4.1.3.2 Non-anti-microbial effects

Co-trimoxazole has beneficial effects in patients with granulomatous polyarteritis[26] which are greater if treatment is started early and are not related to infection[27]. These potentially immunomodulatory effects have been poorly studied. Sulfamethoxazole has a structure similar to other sulphonamides, such as dapsone and sulphapyridine, which are known to have effects on neutrophil chemotaxis[28] and superoxide production[29]. *In vitro* studies have shown that co-trimoxazole or its individual components (trimethoprim and sulfamethoxazole) inhibit neutrophil post-phagocytic myeloperoxidase-mediated protein iodination[30]. In other studies, assessing the effects of different antimicrobial agents on neutrophil respiratory burst, co-trimoxazole and trimethoprim inhibited the chemiluminescence response at therapeutic concentrations[31 32].

Oxidant stress has been implicated in alveolar epithelial injury[33] and epithelial-mesenchymal transition[34] and IPF patients have increased concentrations of 8-isoprostane in exhaled breath condensate[35]. Neutrophils have an important role in causing oxidant stress in IPF[36], and neutrophilic alveolitis features frequently[37]. Furthermore, higher neutrophil counts in sputum are associated with worse lung function[38] and the percentage of bronchoalveolar lavage fluid (BALF) neutrophils at diagnosis is an independent predictor of mortality[39].

Thus, co-trimoxazole may inhibit neutrophil activation and reduce neutrophil-derived oxidative stress. These potential non-anti-microbial effects of co-trimoxazole would be predicted to have beneficial effects in IPF, independently of and/or in addition to its anti-microbial actions.

4.1.4 Risk and Benefits

Co-trimoxazole has been licensed and prescribed to patients with respiratory disease for decades, and hence the risks of this drug are well established. Many patients with human immunodeficiency virus (HIV) receive long-term co-trimoxazole prophylaxis against *Pneumocystis* without serious side effects.

Careful monitoring and exclusion criteria, with optional dose reduction, will minimise the side effect risk in the present study.

The drug is contra-indicated in patients with hypersensitivity to sulphonamides or trimethoprim and in those with severe liver or renal failure and in infants, all of which are reflected in the exclusion criteria. Serious risks include hypersensitivity reactions, bone marrow depression (reduced by co-administration of folic acid) and crystalluria (reduced by adequate fluid intake) all of which occur extremely rarely. In TIPAC[15], co-trimoxazole, when compared to placebo, increased gastrointestinal side effects (44.6% vs. 24.4%), rash (15.2% vs. 4.7% (3% and 1% attributed to study medication)) and serum creatinine. There were no significant differences in other effects that could be adverse effects of active drug treatment. There is a well-recognised risk of drug interactions which will be managed by increased monitoring or drug exclusion. There is a theoretical risk of the development of antimicrobial resistance, however co-trimoxazole is already prescribed on a long term basis for the prophylaxis of *Pneumocystis jirovecii* infection and IPF is sufficiently uncommon that any selection in IPF patients will make a tiny addition to the total resistance burden in the population.

The benefits of co-trimoxazole are less well known but potentially large. The benefits previously identified were improvements in lung function and exercise capacity in one study and reductions in respiratory related hospital admissions or deaths in patients with impaired lung function in another study.

4.1.5 Rationale for current study

As TIPAC[15] was powered to detect differences in FVC, analysis of all other outcome measures was exploratory. Furthermore, UK prescribing practices in IPF have changed since TIPAC was completed, with cessation of corticosteroid treatment and commencement of pirfenidone. An evaluation of efficacy by a clinical trial that is adequately powered to detect clinically important differences on clinically relevant endpoint is required before this treatment can be considered in clinical practice. In addition, it is important to explore the mechanism of action of co-trimoxazole so that this medication can be suitably targeted, newer therapies considered and further studies designed.

4.2 Aim and Objectives

The main aim of the study is to determine the clinical efficacy of co-trimoxazole. Secondary mechanistic aims are to investigate the effect on 1) the lung microbiota and other measures of infection, 2) markers of epithelial injury and 3) markers of neutrophil activity. An exploratory aim is to determine whether the mechanistic properties relate to clinical efficacy.

4.2.1 Primary Objective

To compare the time to death (all causes), lung transplant or first non-elective hospital admission between co-trimoxazole and placebo arms in patients with moderate to severe (forced vital capacity (FVC) ≤75% predicted) IPF during a median treatment period of 27 (range 12 to 42) months.

4.2.2 Secondary objectives

To compare between co-trimoxazole and placebo arms:

1. clinical efficacy in terms of respiratory-related hospital admission, death, health-related quality of life (King's Brief Interstitial Lung Disease questionnaire), quality of life adjusted years, cough score and quality of life, lung function and oxygen saturations

4.2.3 Exploratory mechanistic outcomes

1. blood biomarkers including, but not limited to, those of infection/inflammation (C-reactive protein), disease progression (surfactant protein (SP)-D) and Matrix Metalloproteinase (MMP)-7)) or neutrophil activity (myeloperoxidase (MPO))
2. blood will be taken for genetic testing to determine whether treatment response or adverse event profile is related to any genetic marker.

BALF biomarkers (in a subset of 50 patients undergoing bronchoscopy (25 patients in each treatment group), including but not limited to, the following:

3. change in microbiota
4. change in concentration of neutrophil elastase, MPO or percentage of leukocytes that are neutrophils
5. change in SP-D or MMP-7
6. an assessment of the clinical effects being related to change in microbiology, neutrophil or disease activity/progression markers

5 Trial Design

The study is a Phase III double blind, parallel group, 1 to 1 randomised placebo controlled multi-centre clinical superiority trial of oral co-trimoxazole versus placebo in 330 patients with moderate to severe (FVC <=75% predicted) IPF, with outcomes assessed during a median treatment period of 27 (range 12-42) months. Randomisation will be performed centrally according to a computer-generated randomisation code with secure e-mail correspondence by NCTU to research pharmacists only. Minimisation factors are: research site, whether patients undergo a baseline bronchoscopy and use of baseline licensed medication for IPF. A subgroup of 50 patients (randomised on a 1:1 basis to receive active and placebo treatments) will undergo a bronchoscopy for bronchoalveolar lavage according to British Thoracic Society Guidelines[47].

6 Methods

6.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to the chief investigator.

6.1.1 Study Setting

The study will be conducted primarily in academic hospitals within the United Kingdom

6.1.2 Site/Investigator Eligibility Criteria

Sites will be specialist interstitial lung disease centres, meet the specifications required for specialist interstitial lung disease (ILD) centre status or work in association with specialist centres. Sites will have the facilities for research staff to undertake all of the measurements and store the samples required for the study unless, in exceptional circumstances, an approval that the site is excluded from some aspects of the study is granted by the Chief Investigator prior to site enrolment.

Once a site has been assessed as being suitable to participate in the trial, and accepted by the Chief Investigator as a recruitment site, the trial team will provide them with a copy of this protocol and the EME-TIPAC Trial Master File (TMF) documentation to use when applying local institutional approval.

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The local principal investigator is responsible for the conduct of the study at his/her site and for the safety and medical care of study patients. Both the investigator and local trust legal representative will be required to sign the site agreements. Specific requirement are to comply with the trial protocol, maintain appropriate qualifications and familiarity with the summary of product characteristics of co-trimoxazole, comply with the principles of GCP, maintain the local site file, permit monitoring and audit as necessary at the site, and maintain documented evidence of all staff at the site who have been delegated significant trial related duties including a record of their training.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return to NCTU.

6.2 Site approval and activation

The Clinical Trial Authorisation (CTA) for the trial requires that the Medicines and Healthcare products Regulatory Agency (MHRA) is supplied with the names and addresses of all participating site Principal Investigators. Trial staff at NCTU will perform this task.

On receipt of the signed site contract, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The Clinical Trial Manager or delegate will notify the Principal Investigator (PI) in writing of the plans for site initiation including training.

The site must conduct the trial in compliance with the protocol. The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at NCTU.

A list of activated sites may be obtained from the Clinical Trial Manager.

6.3 Patients

6.3.1 Eligibility Criteria

6.3.1.1 Participant selection

No exceptions to the stated eligibility criteria will be permitted. Questions about eligibility criteria should be addressed prior to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate patients are entered. Patients not meeting the criteria should not be entered into the trial.

Patients will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

1) Male or female, aged greater than or equal to 40 years

2) A diagnosis of IPF based on multi-disciplinary consensus decision undertaken at a specialist centre (or MDT otherwise meeting the criteria of a specialist centre) following a review of an appropriate clinical history, characteristic features of UIP on thoracic high resolution computed tomography (HRCT) and/or usual interstitial pneumonia (UIP) histology confirmed by surgical lung biopsy according to the latest international guidelines[6].
3) Patients may receive oral prednisolone up to a dose of 10 mg per day (in keeping with previous studies[13]), anti-oxidant therapy, Pirfenidone, Nintedanib or other licensed medication for IPF. 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, to exclude asymptomatic patients.

5) Able to provide informed consent.

6.3.1.3 Participant Exclusion Criteria

1) Forced vital capacity >75% predicted

2) A recognised significant co-existing respiratory disease, defined as a respiratory condition that exhibits a clinically relevant effect on respiratory symptoms and disease progression as determined by the principal investigator following multi-disciplinary discussion. For example,

patients with bronchiectasis will only be included if the bronchiectasis is deemed to be traction bronchiectasis as a result of Idiopathic Pulmonary Fibrosis.

3) Patients with obstructive airways disease defined as forced expiratory volume in 1 second(FEV1)/FVC<60%[41]

4) Patients with 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, will not be eligible because of the difficulty of obtaining reliable baseline lung function.

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 (e.g. serum transaminase > 3 x upper limit of normal (ULN), Bilirubin > 2 x ULN (unless the patient has Gilbert's Syndrome) and renal failure (e.g. creatinine clearance <30ml/min).

6) Patients receiving immunosuppressant medication (except low dose prednisolone) including azathioprine and mycophenolate mofetil. The British Thoracic Society Interstitial Lung Disease Specialist Advisory Group recommend the withdrawal of azathioprine in patients who have disease progression and that it should not be commenced in new incident cases of IPF. Moreover, combining azathioprine with co-trimoxazole increases the potential for patients to develop neutropenia.

7) Female subjects must be of non-childbearing potential, defined as follows: postmenopausal females who have had at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhoea with serum FSH>40mIU/ml or females who have had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy at least 6 weeks prior to enrolment.

8) Known allergy or intolerance to trimethoprim or sulphonamides or their combination for safety reasons.

9) Untreated folate or B12 deficiency. This is to ensure no bone marrow or neurological adverse effects occur with folate therapy to B12 deficient individuals.

10) Known glucose-6-phosphate dehydrogenase (G6PD) deficiency or G6PD deficiency measured at screening in males of African, Asian or Mediterranean descent. Sulphonamides are recognised to increase the risk of haemolysis in individuals with G6PD deficiency. The prevalence of G6PD deficiency is higher in males of African, Asian or Mediterranean descent. However the risk of haemolysis is low even in populations with high prevalence[42].

11) Receipt of an investigational drug or biological agent within the 4 weeks prior to study entry or 5 times the drug half-life, whichever is the 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). Patients with a baseline serum potassium of between 4.7 and 5.0 mmol/L who are 66 years old or over and

taking potassium sparing diuretics are required to have an extra blood test for safety one week after starting trial treatment due to the increased risk of hyperkalaemia.

6.3.1.4 Co-enrolment Guidance

Patients will be excluded if they are in receipt of an investigational drug or biological agent within the 4 weeks (or 5 times the half-life if this is longer) prior to study entry. Patients can be entered into other observational studies given prior agreement from the TMG of both studies.

6.3.1.5 Screening Procedures and Pre-randomisation Investigations

Written informed consent to enter and be randomised into the trial must be obtained from patients after explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific procedures are performed. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care. These may include pulmonary function testing, routine biochemical, haematological and microbiological analysis and bronchoscopy.

6.4 Interventions

6.4.1 Active treatment arm

6.4.1.1 Products and treatment schedule

Co-trimoxazole (generic): 960mg as 2 tablets of 480mg twice a day plus folic acid 5mg once a day.

6.4.1.2 Dispensing

Patients will have investigational medicinal product (IMP) and folic acid dispensed 3 monthly for the first 6 months then 6 monthly. The IMP will be supplied in bottles providing one month's supply. Folic acid will be dispensed from hospital supplies.

6.4.1.3 Dose Modifications and Interruptions

Dose Modifications

Study drug may be reduced to 2 tablets once a day three times a week plus 5mg folic acid once a day three times a week in the following instances;

1) A patient develops gastrointestinal adverse effects or rash.
2) Potassium > 5.0 mmol/l and < 5.5 mmol/l (Grade 1 hyperkalaemia)
3) Any other Adverse Event that in the opinion of the local Investigator requires a dose reduction.

The dosing interval will be to ensure that the dosing is spread throughout the week (e.g. Monday, Wednesday and Friday or equivalent).

Once a patient has had a dose reduction, **no re-escalation will be permitted**, even if the adverse event leading to the reduction resolves.

Dose Interruptions

If a patient forgets to take a dose and it is more than 24 hours after their scheduled dose, they should omit the missed dose and take the next dose when it is due. Patients must not take a double dose to make up for a forgotten dose.

Please see section 6.4.8 for information regarding Protocol Treatment Discontinuation

6.4.2 Placebo arm

6.4.2.1 Products and treatment schedule

Placebo tablets (manufactured to appear identical to co-trimoxazole 480mg) 2 oral tablets twice a day plus folic acid 5mg once a day.

6.4.2.2 Dispensing

The EME-TIPAC trial is double blinded study and so dispensing for the placebo arm will be managed identically to the active arm (See section 6.4.1.2)

6.4.2.3 Dose Modifications and Interruptions

The EME-TIPAC trial is double blinded study and so all dose modifications, interruptions, and discontinuations for the placebo arm will be managed identically to the active arm (See section 6.4.1.3)

6.4.3 Accountability

The local PI will be responsible for drug accountability at each site. This task will usually be delegated to the site research pharmacist. Accountability will include records of drug and placebo received at site, dispensed to participant, and unused returns, and will ensure batch recall is possible in the event of it being necessary.

6.4.4 Compliance and Adherence

Compliance to study treatment in the form of returned tablet counts will be monitored as part of drug accountability at each visit.

6.4.5 Concomitant Medication

Patients are permitted to receive acetyl cysteine and anti-oxidants, prednisolone (up to a dose of 10mg per day) and licensed treatments for Idiopathic Pulmonary Fibrosis. Patients must be on stable doses of medication for IPF for at least 6 weeks prior to the start of the study. All concomitant medication will be recorded at baseline and change in concomitant medication will be recorded at each visit.

Patients are permitted to receive other medications (e.g. for other conditions), but non-permitted therapies include: amiodarone, azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, D-penicillamine, colchicine, clozapine, methenamine, dapsone gamma-interferon, ciclosporin, mercaptopurine, repaglinide, pyrimethamine, lamivudine, typhoid vaccination or unlicensed medication.

Therapy requiring caution or increased monitoring include: digoxin, warfarin, phenytoin, sulphonylureas and procainamide hydrochloride. Increased monitoring of potassium required if patients commenced on medication which increases serum potassium concentration.

Patients with a baseline serum potassium of between 4.7 and 5.0 mmol/L who are 66 years old or over and taking potassium sparing diuretics (including angiotensin converting enzyme inhibitors or angiotensin receptor blockers), are required to have an extra blood test for safety one week after starting trial treatment due to the increased risk of hyperkalacemia.

If this shows an increase of serum potassium to ≥5.0 mmol/L then dose reduction / discontinuation rules should be followed (see sections 6.4.1.3 and 6.4.8).

In addition increased monitoring of potassium may be required if patients commence potassium sparing diuretics during trial treatment.

6.4.6 Side-effects of Trial Medication

6.4.6.1 Side-effects of Co-Trimoxazole

The following side effects are those included as undesirable effects in the Summary of Product Characteristics for co-trimoxazole.

Very Common (≥1/10) : hyperkalaemia

Common (≥1/100) : nausea, diarrhoea, headache, mild skin rash, monilial overgrowth

Uncommon (≥1/1000) : vomiting

Very rare (≥1/10,000) : glossitis, stomatitis, anorexia, severe skin rash including Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, liver damage (including elevation of serum transaminases, bilirubin levels, cholestatic jaundice and hepatic necrosis), pancreatitis, antibiotic-associated colitis, myocarditis, cough and shortness of breath, pulmonary infiltrates, aseptic meningitis, depression, convulsions, peripheral neuropathy, ataxia, tinnitus, vertigo, hallucinations, hypoglycaemia, blood disorders (including leucopenia, neutropenia, agranulocytosis, thrombocytopenia, megaloblastic anaemia, aplastic anaemia, anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis (in certain G-6-PD deficient patients), hyponatraemia, renal disorders including interstitial nephritis, serum sickness, anaphylaxis, allergic myocarditis, angioedema, drug fever, arthralgia, myalgia, vasculitis, polyarteritis nodosa, systemic lupus erythematosus.

6.4.6.2 Side-effects of Folic Acid

The following side effects are those included as undesirable effects in the Summary of Product Characteristics for folic acid

Uncommon (≥1/1000) : anorexia, nausea, abdominal distension, flatulence, allergic reactions comprising erythema, rash, pruritis, urticarial, dsypnoea and anaphylactic reactions including shock.

6.4.7 Overdose of Trial Medication

Symptoms of over-dosage may include dizziness, nausea, vomiting, rashes, headache, ataxia, drowsiness, dysuria, swelling of the face, weakness and confusion. Bone marrow depression has been reported in acute trimethoprim over-dosage.

Treatment is symptomatic. Observe the patient for at least four hours and monitor U&Es and full blood count in symptomatic cases. Give fluids to maintain a good urine output, increased fluid intake will increase the elimination of sulfamethoxazole, but decrease that of trimethoprim. Calcium Leucovirin 5-10mg daily or calcium folinate 3-6mg of 5-7 days by mouth or IM will counteract the adverse effects of trimethoprim on bone marrow suppression. Other measures as indicated by the patient's clinical condition.

Overdose of folic acid does not require any special procedures or antidotes.

6.4.8 Protocol Treatment Discontinuation

In consenting to the trial, patients are consenting to trial treatments, trial follow-up and data collection. However, an individual participant will stop treatment early or be stopped early for any of the following reasons:

- Any Non-Elective Hospitalisation or Lung Transplant (due to meeting a primary endpoint)
- Serum Potassium of > 5.5 mmol/l
- Co-trimoxazole related haematological disease (e.g. blood dyscrasia or thrombocytopaenia)
- Unacceptable treatment toxicity or adverse event
- Inter-current illness that prevents further treatment
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment by the participant

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Patients who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis, unless they request otherwise.

However patients who are admitted to hospital non-electively will be deemed to have met the primary endpoint. From that point onwards patients will cease to have follow up measurements but survival status will be reported until the end of the study.

6.5 Outcomes

6.5.1 Primary Outcomes

The primary outcome will be the time to death (all causes), transplant or first non-elective hospital admission. This is defined as the time from randomisation to death, lung transplant or first non-elective hospital admission for any reason.

6.5.2 Secondary Outcomes

The individual components of the primary outcome: time to death (all causes) or transplant and time to first non-elective hospital admission, will be analysed separately as secondary outcomes. In addition, respiratory related events will be analysed separately from non-respiratory related events.

Additionally, the following measurements will be undertaken at baseline, 3 and 6 months post randomisation, then 6 monthly for the duration of the study plus at the end of study/hospitalisation:

- Health related quality of life using (i) the King's Brief Interstitial Lung Disease (K-BILD) health related quality of life questionnaire; (ii) the MRC Breathlessness Score; (iii) the EQ5D quality adjusted life year's assessment; (iv) cough score; (v) global rating of concept scale.
- Lung function assessment by spirometry and total lung diffusing capacity of carbon monoxide (DLCO)

Every effort will be made to collect data at time-points with 2 weeks either side up until 6 months then 1 month either side thereafter however data collected out with these time-points will also be captured.

The following measurements will be undertaken at baseline, after 3, 6 and 12 months and at the end of study/hospitalisation (ideally within a 1 or 2 month window (as above)):

- Venous blood analysis for biomarkers if guided by the findings of the BALF analysis below. This may include, but are not limited to, C-reactive protein (CRP), surfactant protein (SP) –D, Matrix Metalloproteinase (MMP)-7, myeloperoxidase.

The following will be undertaken as clinically indicated at any visit:

- Routine microbiology on sputum and nasal swabs

The following will be undertaken at baseline and 12 months

- Leicester cough questionnaire
- Global rating of change – quality of life

The following will be undertaken at baseline 6 weeks, 3, 6, 9 and 12 months then 6 monthly for the duration of the study plus at the end of study/hospitalisation (ideally within a 1 or 2 month window (as above)):

- Full blood count and differential white cell count
- Urea and electrolytes
- Liver function

Unless the patient is otherwise due to attend a clinic visit at the 6 week and 9 month time-points as part of their standard care, the safety bloods for these visits can be performed at the patients GP surgery and the patient followed up via telephone (to check for adverse events and any change in concomitant medication).

In a subset of 50 patients who agree to bronchoscopy BALF will be obtained at baseline between 10 and 17 weeks after starting treatment (preferably at the 3 month visit) and if being undertaken for clinical reasons during an admission to hospital for:

- Molecular analysis including but not limited to high throughput sequencing of DNA derived from bacterial 16S ribosomal RNA genes
- Differential cell count
- Quantitative microbiology culture
- Polymerase chain reaction (PCR) for *Pneumocystis jiroveci* identification
- Alveolar epithelial cell injury markers including SP-D, MMP-7
- Neutrophil activity markers including myeloperoxidase, neutrophil elastase
- Collagen turnover markers including pro-collagen III N-terminal peptide (PIIINP)

6.6 Participant Timeline

6.6.1 Early Stopping of Follow-up

If a participant chooses to discontinue their study drug, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They

should be invited to continue follow up in the trial even though they no longer take the study drug. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected and the participant withdrawn entirely from the trial. NCTU should be informed of the withdrawal in writing using the appropriate EME-TIPAC trial documentation. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all patients who stop follow up early.

Patients who stop study drug will not be replaced.

6.6.2 Participant Transfers

If a participant moves from the area making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed at another participating trial centre. Written consent should be taken at the new centre and then a copy of the participant's CRFs should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete.

6.6.3 Loss to Follow-up

Sites will be asked to account for the vital status and details of admission to hospital for all patients who have consented to participate in the study regardless whether they have withdrawn from the intervention or study assessments. Patients will be asked to provide consent so that follow up information on overall or hospital free survival can be obtained from medical records using the NHS number e.g. through their GP or the Health and Social Care Information Centre if required.

6.6.4 Trial Closure

The end of the trial will be defined as 12 months following the last trial visit of the last patient randomised.

6.7 Sample Size

The primary outcome measure is the time to death (all causes), transplant or first non-elective (all cause) hospital admission. With 264 patients randomised over a period of 30 months and an additional 12 months follow-up after the last patient is recruited (a total of 42 months after the first patient was enrolled, median patient study duration of 27 months), giving us 96 events the trial will have 80% power (two-sided test, significance level of 5%) to show a change in hospitalisation free survival from a median value of 28.8 months in the control arm to 51.1 months in the co-trimoxazole arm (hazard ratio of 0.56) using a log rank test. This is based on a sensitivity analysis of patients from TIPAC with reduced lung function (FVC<70% predicted) using an intention to treat analysis.

With regard to the power of the serum biomarkers, assuming that 264 will provide data for the mechanistic aspect, the study will provide 80% power to detect a difference of 6.7 mg/dl in CRP based on a standard deviation (SD) of 19.38[43], of 0.51 ng/ml in MMP-7 based on a SD of 1.48[44] and of 99 ng/ml in SP-D based on a SD of 212ng/ml[45]. It is impossible to undertake a power calculation for the change in the microbiota. However co-trimoxazole is effective against many of the organisms detected in BAL from routine culture and genotyping techniques and therefore it is anticipated that, within a proposed group of 50 patients, a change in the flora will be detected

6.8 Recruitment and Retention

6.8.1 Recruitment

Patients will be identified mainly by review of ILD multi-disciplinary team (MDT) meeting minutes or summaries. Identification will also be via screening patient registries, hospital medical records and databases of research interested patients or clinical details. Recruitment strategies may include any of the following:

- Patients will be approached by the clinical care team directly when they attend the hospital outpatient clinic who will give an invitation letter on hospital headed which provides an overview of the study and a patient information leaflet. The clinic staff will arrange a subsequent recruitment visit.
- The clinic team may also mail an invitation letter with or without a patient information sheet along with a reply form detailing a range of methods for the interested potential patients to contact the local trial team to arrange a screening appointment.
- Where patients are due to attend clinic for a routine appointment in the near future, the clinical care team may mail an invitation letter on hospital headed paper which provides an overview of the study, and a patient information sheet, so that the patient receives these documents at least 24 hours in advance of the forthcoming routine clinic assessment visit. After the participant has provided written informed consent, screening for eligibility and baseline assessments will be undertaken at the routine clinic visit.
- For centres with access to a volunteer database, the researchers may mail the invitation letter and reply form directly to the volunteer.

Potential patients may be contacted by phone between 3 and 7 days after the mailing of the letter to ensure that they have received it.

Consent will be obtained prior to any study related procedure. Following consent, screening bloods will be taken and other eligibility will be assessed. Patients meeting all entry criteria (after review of screening bloods) may be randomised without a subsequent visit. Medication will be dispensed by hospital pharmacy to the patient or via a courier. Medication sent by courier (or other signed for delivery service) to participants, will require signature on receipt. Participants will be advised to store their medication below 25°C but there will be no temperature monitoring after dispatch from the third party.

6.8.2 Retention

This study is designed to follow routine care as much as possible and the study visits are intended to coincide with routine clinical follow-up visits for patients with IPF. Patients will be given a card with the contact details of the local PI that will request details of hospital admissions to be reported. Patients will be asked to provide informed consent for their contact details to be stored in a trial contacts database at UEA. Patients can withdraw consent to this in writing at any time.

6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation

The allocated treatment for a patient will be generated via computer written code using minimisation. Minimisation will be performed using Taves' method with the factors measured at baseline: i) study site, ii) Bronchoscopy (yes/no); iii) and licensed medication for IPF (yes/no). In order to decide on the treatment allocation the code will calculate the number of patients in each group that have the same characteristics as the patient awaiting allocation; they will be allocated to the intervention with the smaller number with a high probability. If the numbers are the same then simple randomisation is used.

Full details of the minimisation algorithm (including the probability of allocation) will be documented in a separate document (called Randomisation plan for EME-TIPAC) stored in a shared file accessible to only the study statistician and database manager.

6.9.1.2 Allocation Implementation

The patients will be allocated to the intervention by a process embedded in the web-based data Management system. The randomisation code will be saved in the study database for later decoding and also for emergency unblinding purposes. When a patient is randomised an email will be sent to the appropriate local pharmacy for the patient, who will prepare the medication pack.

6.9.2 Blinding

This will be double blind study. The placebo and active treatments will appear identical and will be dispensed in identical containers. All trial patients, care providers, outcome assessors and data analysts will remain blind throughout the study.

6.9.3 Emergency Unblinding

The decision to unblind a single case should be made when knowledge of an individual's allocated treatment is required:

· To enable treatment of severe adverse event/s, or

· In the event of an overdose

Where possible, requests for emergency or unplanned unblinding of individuals should be made via the trial manager and agreement of the Chief Investigator will then be sought. However, in circumstances where there is insufficient time to make this request or for agreement to be sought, the treating clinician should make the decision to unblind immediately. This will be done via the study database (local PIs and the CI will have special logins which will allow unblinding and which will be closely audited within the database management system) or by contacting Dr Andrew Wilson who will authorise unblinding by the Data Management Team. All instances of unblinding should be recorded and reported to NCTU by the local principal investigator, including the identity of all recipients of the unblinding information.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Data collection will be by direct online entry of data onto the central online database by delegated members of research site staff. Staff will receive training on data collection and use of the online system. Identification logs, screening logs and enrolment logs will be kept locally, either in paper or

electronic form. Routine clinical data including lung function, immunology and radiological and histological images pertinent to the diagnosis of IPF may be collected.

6.10.2 Non-Adherence and Non-Retention

The consent form will explain that if a participant wishes to withdraw from the study the data and samples acquired prior to that point will be retained. Reason for withdrawal will be recorded, if given, as will loss to follow up.

Non adherence to trial medication will be assessed through tablet counts of unused returned drug supplies at each study visit.

6.10.3 Data Management

Within each trial site patients will be allocated a unique trial Participant Identification Number (PIN). Data will be entered under this identification number onto the central database stored on the servers based at UEA. The database will be password protected and only accessible to members of the EME-TIPAC trial team at NCTU, the participating hospitals and external regulators. The server is in a secure room, which is protected by CCTV, where access is restricted to members of the UEA Information Systems team by security door access. The study database will be built using Microsoft SQL Server tools and direct access will be restricted to NCTU data management staff. Data entry will be via web pages created using Microsoft.NET technology. All internet traffic will be encrypted using the standard SSL (Secure Sockets Layer) methodology. The data entry system will validate data on entry to ensure it is of the expected type (e.g. integers, dates etc.) and range of values. Periodically and at database lock the data will be further validated for errors and inconsistencies. The database is linked to an audit tool where all data additions, modifications and deletions are recorded with date/time and the user ID of the person making the change. The database is designed to comply with the ICH Guideline for Good Clinical Practice (GCP), within the Standard Operating Procedures for Data Management in NCTU and also where appropriate with UEA IT procedures.

The database and coding values have been developed by the Head of Data Management in conjunction with the study statistician and other NCTU members. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data. Further details can be found in the EME-TIPAC Trial Data Management Plan. After completion of the trial the database will be retained on the servers of UEA for 5 years for on-going analysis of secondary outcomes.

The identification, screening and enrolment logs, linking participant identifiable data to the pseudoanonymised Participant Identification Number, will be held locally by the research sites and potentially at NCTU. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for a minimum of 5 years.

6.10.4 Statistical Methods

6.10.4.1 Statistical Analysis Plan

A full SAP will be produced and agreed with both the TSC and DMC prior to the analysis of any data.

6.10.4.2 Statistical Methods – Outcomes

Primary outcome

- Time from randomisation to death (all causes), lung transplant or first non-elective hospital admission for any reason.

Secondary efficacy outcomes

- Time from randomisation to death (all causes)
- Time from randomisation to first non-elective hospital admission for any reason
- Time from randomisation to lung transplantation.
- (i) the King's Brief Interstitial Lung Disease (K-BILD) health related quality of life questionnaire; (ii) the MRC Breathlessness Score; (iii) the EQ5D quality adjusted life year's assessment, (iv) cough score and quality of life (Leicester cough questionnaire (LCQ)).
- Lung function including assessment by spirometry and total lung diffusing capacity of carbon monoxide (DLCO)

Secondary outcome measures for safety (measured at local hospital laboratories)

- Full blood count
- Urea and electrolytes
- Liver function
- Adverse Events including SAEs

Further exploratory and mechanistic outcomes

Analysis of blood biomarkers will be undertaken depending on the results of the BALF (below).

Results of routine microbiology and high-throughput sequencing will be presented descriptively by tabulating the different types of microbiological cultures and the number.

6.10.4.3 Additional Analyses - Subgroup

A subgroup analysis by disease duration (new – within 2 years of diagnosis vs old – more than 2 years of diagnosis)

6.10.4.4 Additional Analyses

In addition to the efficacy analyses, analyses will be undertaken which will attempt to correlate the change in clinical outcomes with the change in mechanical parameters at the final time point they are both measured. A similar approach will be undertaken to identify which of the factors are predictive of change in microbiota.

6.10.4.5 Analysis Population and Missing Data

The analyses population are defined as:

a) intention-to-treat: all randomised individuals regardless of adherence

b) per-protocol: all randomised individuals who adhere to the study medication to within 80% (based on pill counts)

c) modified-per-protocol: all randomised individuals who adhere to the high-dose regime.

d) safety population: all patients randomised who received at least one dose of the study treatment.

The primary outcome analysis should not be subject to missing data, although they will be due to right censoring this is explicitly allowed for in the analysis.

Missing data that occurs in secondary and mechanistic outcomes will be multiply imputed to increase precision of the treatment effect estimates. Sensitivity analyses will be conducted to assess the impact of the multiple imputations and a complete case analysis will also be conducted. All imputations will be examined to ensure sensible values are being generated. Imputation models will contain baseline measures, outcome measures and factors predictive of missing data.

Individuals who have met the primary endpoint or have withdrawn consent for collection of any outcome will be censored at the last observation point for example data on the time until first hospitalisation will be censored at the time of death (if death occurs).

6.10.4.6 Efficacy Analyses

The primary outcome will be analysed using a Cox proportional hazards model adjusted for the variables included in the minimisation algorithm (bronchoscopy, baseline licensed IPF medication, site). The results will be presented as the Kaplan-Meier estimate of the survival function for each treatment arm separately and if appropriate the median will be estimated. The treatment effect size will be the hazard ratio and estimated with 95% confidence intervals and p-value.

The time until death and time until non-elective hospital admission will be analysed using Cox proportional hazards models adjusted for the variables included in the minimisation algorithm, (bronchoscopy, baseline licensed IPF medication, site). The results will be presented as the Kaplan-Meier estimates of the survival functions for each treatment arm separately and if appropriate the medians will be estimated. The treatment effect sizes will be the hazard ratios and estimated with 95% confidence intervals and p-value.

At each relevant time point after 6 weeks post randomisation, the K-BILD, EQ5D, LCQ, spirometry (FVC per cent predicted, FEV per cent predicted, FVC absolute value, FEV absolute value and FVC/FEV ratio) and DLCO will be analysed using linear model to compare the average values between the treatment arms adjusted for the variables included in the minimisation algorithm, bronchoscopy and baseline, site will be included as a random effect. The effect size will be the mean difference and will be presented with 95% confidence intervals and p-values.

In addition to the above a repeated measures model will be done including all post-randomisation observation for all individuals. An additional random effect for patient will be included in the model.

The MRC Breathlessness Score and cough score will be analysed using a Mann-Whitney test to compare the distribution of the score between the treatment arms. A generalized effect size will be estimated and presented with 95% confidence intervals and a p-value.

6.10.4.7 Safety Analyses

The safety analysis will be based on the pre-defined population (as above). Summary tables will be presented for incidence rates (number of patients with at least one incidence) of adverse events and

SAEs coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Tables of change from baseline will be presented for the blood and other clinical laboratory assessments.

6.10.4.8 Mechanistic Analyses

From the stored blood the proposed analyses, which is subject to change depending on the results of the bronchoscopy results. The same linear mixed model for the analysis of K-BILD will be used for the biomarkers.

The analysis of routine microbiology and the results of the high-throughput sequencing will be descriptive by tabulating the different types of microbiological cultures and the number.

The BAL will also provide data on biomarkers including myeloperoxidase, SP-D, MMP-7, neutrophil elastase and PIIINP these will be compared using the same linear mixed model for the analysis of K-BILD. Those biomarkers which are significant at the p=0.1 level will then be measured in the stored blood sample for everyone and compared between the two treatment arms.

6.11 Data Monitoring

6.11.1 Data Monitoring Committee

Details of the roles and responsibilities of the Data Monitoring Committee (DMC), including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the EME-TIPAC DMC Terms of Reference (ToR).

6.11.2 Interim Analyses

There is no plan for an interim analysis of EME-TIPAC data.

6.11.3 Data Monitoring for Harm

Adverse events will be collected at each visit and analysed according to the Statistical Analysis Plan. Adverse events by treatment group will be reviewed regularly by the Data Monitoring Committee as described in their Terms of Reference.

6.11.3.1 Safety reporting

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial.

Table 1: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death* • is life threatening** • requires hospitalisation or prolongs existing hospitalisation*** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition****

* Death in this trial forms part of the primary endpoint and consequently does not constitute an SAE **unless the death was treatment related** in the opinion of the local investigator.

** the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction)

*** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation in this trial forms part of the primary endpoint and consequently does not constitute an SAE **unless the hospitalisation was treatment related** in the opinion of the local investigator.

**** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

Adverse events include:

- an exacerbation of a pre-existing illness **which is considered to be treatment related**
- an increase in the frequency or intensity of a pre-existing episodic event or condition
- a condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after trial drug administration. (This does not include pre-existing conditions recorded as such at baseline – as they are not detected after trial drug administration.)
- continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery
- Overdose of medication without signs or symptoms
- an exacerbation of a pre-existing illness **which is not considered to be treatment related**

Hospitalisations and Deaths which do are not related to trial treatment, and therefore do not require reporting as SAEs for the trial, must be recorded on the EME-TIPAC eCRF Database within 7 days of the site becoming aware.

6.11.3.2 Other Notifiable Adverse Events

Folic acid in the EME-TIPAC trial is classified as a Non-IMP. There is no requirement to report adverse reactions to the n-IMP alone, but reporting is required when there is a suspected interaction between the IMP and n-IMP as a SUSAR and for this reason notification of adverse events due to suspected interactions between folic acid and co-trimoxazole as an SAE (see 6.11.3.4). Where a serious adverse reaction to folic acid is observed sites are encouraged to report to the marketing authorisation holder.

6.11.3.3 Procedures to follow in the event of female patients becoming pregnant

Female subjects must be of non-childbearing potential, defined as follows: postmenopausal females who have had at least 12 months of spontaneous amenorrhea 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.

6.11.3.4 Investigator responsibilities relating to safety reporting

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes and reported in the case report form.

All SARs, and SAEs that do not relate to trial endpoints, including any that result from a possible interaction between co-trimoxazole and folic acid, (i.e. the reaction cannot clearly be attributed to the folic acid alone) should be should be notified to NCTU immediately the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

As death and non-elective hospital admission forms part of the primary endpoint for the trial, hospital admission will not be reported as an SAE unless the death or non-elective hospital admission was treatment related, in the opinion of the local investigator.

This information must however be recorded on the eCRF Database within 7 days of the site becoming aware.

6.11.3.4.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 1. If the event is classified as a SAR, or a SAE that does not relate to a trial endpoint, then an SAE form must be completed and NCTU (or delegated body) notified within 24 hours.

6.11.3.4.2 Relatedness

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 2.

As this is a placebo-controlled trial, the evaluation of causality must be performed as if the patient is on active treatment.

Table 2: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE

Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	SAR
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out	SAR

If an SAE is considered to be related to trial treatment, and treatment is discontinued, interrupted or the dose modified, refer to the relevant Interventions sections of the protocol.

6.11.3.4.3 Expectedness

If there is possible, probable or definite involvement of the trial medications (including any comparators), the sponsor or delegate will assess the expectedness of the event. An unexpected adverse reaction is one that is not reported in the current SPCs, or one that is more frequently reported or more severe than previously reported. If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) and MHRA and REC reporting guidelines apply (see Notifications sections of the protocol).

6.11.3.4 Notifications

6.11.3.4.1 Notifications by the Investigator to NCTU

NCTU must be notified of all SAEs within 24 hours of the investigator becoming aware of the event.

Investigators should notify NCTU of any SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to NCTU until trial

closure. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system (https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/).

The initial SAE form should be completed by a member of the study team named on the delegation log as taking responsibility for this role with attention paid to causality. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to NCTU. Detailed written reports should be completed as appropriate. Systems should be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

The SAE form must be scanned and sent by email to the NCTU SAE reporting email address:

nctu.safety@uea.ac.uk

Patients must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to NCTU as further information becomes available. Additional information and/or copies of test results etc. may be provided separately. The participant must be identified by trial number, date of birth and initials only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

6.11.3.4.2 NCTU responsibilities

Medically qualified staff at NCTU and/or the Chief Investigator (CI or a medically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality assessment given by the local investigator and the CI, both opinions and any justifications will be provided in subsequent reports.

The delegated staff at NCTU will make an initial assessment of expectedness which will be confirmed by the CI.

NCTU is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA and competent authorities of other European member states and any other countries in which the trial is taking place) and the RECs as appropriate. Fatal and life threatening SUSARs must be reported to the competent authorities within seven days of NCTU becoming aware of the event; other SUSARs must be reported within 15 days.

NCTU will keep investigators informed of any safety issues that arise during the course of the trial.

NCTU will submit Development Safety Update Reports (DSURs) to competent authorities.

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the EME-TIPAC trial are based on the standard NCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of patients; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

6.11.4.2 Central Monitoring at NCTU

NCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the EME-TIPAC trial Data Management Plan.

Patients are consented to enable the NCTU to hold a copy of the consent form for the trial to facilitate central data monitoring.

6.11.4.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the EME-TIPAC Quality Management and Monitoring Plan (QMMP). The QMP will also detail the procedures for review and sign-off of monitoring reports.

6.11.4.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

6.11.4.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect patients, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the NCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the EME-TIPAC Quality Management and Monitoring Plan.

6.11.4.4.1 Trial Management Team

The Trial Management Team (TMT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMT terms of reference.

6.11.4.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

6.11.4.4.3 Trial Steering Committee

The Trial Steering Committee (TSC) is the group responsible for oversight of the trial in order to safeguard the interests of trial patients. The TSC provides advice to the CI, NCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

6.11.4.4.4 Data Monitoring Committee

The Data Monitoring Committee (DMC) is the only oversight body that has access to unblinded accumulating comparative data. The DMC is responsible for safeguarding the interests of trial patients, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the DMC terms of reference. The DMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

6.11.4.4.5 Trial Sponsor

The sponsor of the trial is the Norfolk and Norwich University Hospitals Foundation Trust. Formal agreements are in place for sponsor activities that are delegated to the University of East Anglia and the NCTU.

7 Ethics and Dissemination

7.1 Research Ethics Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local Research and Development (R&D) approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind

at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

7.2 Competent Authority Approvals

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK. This protocol will be submitted to the Medicines and Healthcare products Regulatory Agency.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the Competent Authority, regulatory agency or equivalent in accordance with relevant national and local requirements and practices.

7.3 Other Approvals

The protocol will be submitted to the relevant R&D department of each participating site. A copy of the local R&D approval (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the co-ordinating centre before patients are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the NCTU Protocol Review Committee.

7.4 Protocol Amendments

Substantial protocol amendments will be co-ordinated by the EME-TIPAC trial team at NCTU after approval by the TSC. Investigators and other relevant parties will be notified of amendments in a timely manner so as to ensure appropriate regulatory and ethical principles are met. A summary of protocol amendments will be maintained within the protocol.

7.5 Consent or Assent

During the consent process it will be made clear that the participant can decline to participate in all or any aspect of the trial, at any time and for any reason, without affecting their future care and treatment.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use.

A copy of the approved consent form is available from the NCTU trial team. Patients are specifically asked for consent for the NCTU to collect and retain a copy of the signed consent form.

A subgroup of patients will be invited so that 50 patients will undergo bronchoscopy for the purposes of obtaining bronchoalveolar lavage fluid. Bronchoscopy with BAL is safe in patients with IPF with a risk of serious adverse events of <1:1000 at experience sites. In a study of 281 patients with ILD undergoing BAL no events required therapy[46]. Bronchoscopies will be performed as per current British Thoracic Society Guidelines[47] by an experienced bronchoscopist. Specific consent will be requested for this procedure. Patients can refuse to take part in the bronchoscopy substudy but remain eligible for the main trial.

All patients will be invited to provide a sample of blood for DNA analysis. Specific consent will be requested for this substudy. Patients can refuse to take part in the substudy but remain eligible for the main trial.

All patients will be asked to provide written informed consent for long term follow-up using routinely collected data and appropriate linkage to allow this data to be best used.

7.6 Confidentiality

Within each trial site patients will be allocated a unique trial PIN. The co-ordinating centre and each site will maintain a password protected encrypted database/spreadsheet which enables linkage of the PIN to the participant's name, contact details and hospital/NHS number.

7.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

7.8 Indemnity

The NHS indemnity scheme will apply to the potential liability of the sponsor for harm to participants arising from the management and conduct of the research.

7.9 Finance

The EME-TIPAC trial is fully funded by National Institute for Health Research Efficacy and Mechanism Evaluation Programme Grant number 12/206/09.

7.10 Archiving

The investigators agree to archive and/or arrange for secure storage of EME-TIPAC trial materials and records for a minimum of 5 years after the close of the trial unless otherwise advised by the NCTU.

7.11 Access to Data and samples

Requests for access to trial data and stored samples will be considered, and approved in writing where appropriate, after formal application to the TMG and TSC

7.12 Ancillary and Post-trial Care

There are no plans to offer co-trimoxazole and folic acid to individuals participating in this study after its conclusion.

7.13 Publication Policy

7.13.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect.

7.13.2 Authorship

Ownership of the data arising from the study resides with the trial team. The publication policy will be in line with rules of the International Committee of Medical Journal Editors. The TMG will decide on authorship with any difficulties being resolved by the TSC.

8 Protocol Amendments

This is version 3.0 of the protocol. A summary of protocol amendments is listed in the table below.

Protocol Version	Date	Summary of Changes
1.3	12.12.14	n/a
2.0	02.02.15	• Addition of CTA number, signatures and ISRCRN on cover page • An Exclusion Criteria was added (sections 1.3 and 6.3.1.3) following updated information on the risk of hyperkalaemia in certain patients receiving the trial drug. • Exclusion Criteria were added (sections 1.3 and 6.3.1.3) to include rules on patients receiving antibiotics prior to entering the study. • Minor corrections and clarifications were made to the Time and Events table (Section 1.4) • Removal of a member of the Trial Team and TMG (Sections 1.5.2 and 1.5.3) due to staff changes. • Transfer of a member of the TSC to the TMG (Sections 1.5.4 and 1.5.3) • The Trial Diagram (section 2) was updated and made easier to understand. • Text was added, relating to GCP training requirements for site staff (Section 6.1.2.1) • Increased guidance for Dose Modifications (Sections 6.4.1.3 and 6.4.2.3). • Increased guidance relating to Concomitant Medication (Section 6.4.5). • Additional information was added to the recruitment process (section 6.8.1) relating to the initial supply of drug which is to be sent directly by the site to the patient • Minor Correction to Data Collection Methods (Section 6.10.1) • Clarification relating to the Safety reporting requirements when related to trial treatment (Sections 6.11.3.1 and 6.11.3.4) so that deaths and hospitalisations which are, in the opinion of the local investigator, related to the trial treatment should be reported as SAEs. • Additional guidance on the evaluation of causality (Section 6.11.3.4.2). In addition to the above, minor administrative, typographical and formatting changes have been made throughout the protocol.
3.0	16.05.16	• Modification of Inclusion Criteria 2 to remove the requirement for diagnosis of IPF to be within 2 years of enrolment in to the study (sections 1.3 and 6.3.1.2). • Modification of Exclusion Criteria 1 (sections 1.3 and 6.3.1.3). • Modification of Inclusion Criteria 3 to change the 6 week stable treatment requirement to 4 weeks to match the washout period for other treatments. • Trial Summary updated to include actual Date of First Enrolment (sections 1.3) • Time and Events table (section 1.4) updated to enable the 6 week and 9 month assessments to be performed via GP and a telephone call (if applicable) to reduce patient burden. Additional guidance added for BALF timescales added and increased flexibility to the 6 and 9 month visit windows.

		• Trial Diagram (section 2) updated to represent the changes to the inclusion and exclusion criteria mentioned above • Additional guidance added to Section 6.1.2 regarding Site/Investigator Eligibility Criteria. • Dose discontinuation information in sections 6.4.1.3 and 6.4.2.3 merged in to Protocol Treatment Discontinuation section (6.4.8) • Sections 6.4.2.2 (Placebo Dispensing) and 6.4.2.3 (Placebo Dose Modifications and, Interruptions and Discontinuations) simplified to refer to corresponding sections for active IMP. • Protocol Treatment Discontinuation Section (6.4.8) updated to clarify that patients are to discontinue treatment for Non-Elective Hospitalisation or Lung Transplant (due to meeting a primary endpoint) • Text added to sections 6.11.3.4 and 6.11.3.1 to remind site to record endpoints on the EME-TIPAC eCRF Database within 7 days of the site becoming aware. • Previous SAE reporting email address and fax number in section 6.11.3.4.1 replaced with new NCTU SAE reporting email address In addition to the above, minor administrative, typographical and formatting changes have been made throughout the protocol.

9 References

1. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;**158**(3):200-7
2. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj 2013;**346**:e7586
3. Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 2000;**162**(6):2213-7
4. Navaratnam V, Fleming KM, West J, et al. The rising incidence of idiopathic pulmonary fibrosis in the UK. Thorax 2011;**66**(6):462-7
5. Macpherson KJ, Lewsey JD, Jhund PS, et al. Trends in incidence and in short term survival following a subarachnoid haemorrhage in Scotland, 1986-2005: a retrospective cohort study. BMC Neurol 2011;**11**:38
6. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;**183**(6):788-824
7. Raghu G, Anstrom KJ, King TE, Jr., Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;**366**(21):1968-77
8. Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. New England Journal of Medicine 2005;**353**(21):2229-42
9. Martinez FJ, de Andrade JA, Anstrom KJ, King TE, Jr., Raghu G. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. The New England journal of medicine 2014;**370**(22):2093-101
10. Noth I, Anstrom KJ, Calvert SB, et al. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2012;**186**(1):88-95
11. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011;**377**(9779):1760-9
12. King TE, Jr., Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. The New England journal of medicine 2014;**370**(22):2083-92
13. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011;**365**(12):1079-87
14. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. The New England journal of medicine 2014;**370**(22):2071-82
15. Shulgina L, Cahn AP, Chilvers ER, et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial. Thorax 2013;**68**(2):155-62
16. Varney VA, Parnell HM, Salisbury DT, Ratnatheepan S, Tayar RB. A double blind randomised placebo controlled pilot study of oral co-trimoxazole in advanced fibrotic lung disease. Pulmonary Pharmacology & Therapeutics 2008;**21**(1):178-87
17. Shulgina L, Cahn AP, Chilvers ER, et al. Author's response: co-trimoxazole treatment in idiopathic pulmonary fibrosis. Thorax 2013;**68**(9):884-5
18. Atkins CPL, Y.;Wilson,A.M.;. Outcomes in idiopathic pulmonary fibrosis: a meta-analysis from placebo controlled trials. Respir Med. 2014 Feb;108(2):376-87
19. Müllerova H, Chigbo C, Hagan GW, et al. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. Respir Med 2012;**106**(8):1124-33
20. Olson AL, Swigris JJ, Raghu G, Brown KK. Seasonal variation: mortality from pulmonary fibrosis is greatest in the winter. Chest 2009;**136**(1):16-22
21. Richter AG, Stockley RA, Harper L, Thickett DR. Pulmonary infection in Wegener granulomatosis and idiopathic pulmonary fibrosis. Thorax 2009;**64**(8):692-7
22. Vidal S, de la Horra C, Martin J, et al. Pneumocystis jirovecii colonisation in patients with interstitial lung disease. Clin Microbiol Infect 2006;**12**(3):231-5

23. Garzoni C, Brugger SD, Qi W, et al. Microbial communities in the respiratory tract of patients with interstitial lung disease. Thorax 2013;**68**(12):1150-6 24. Molyneaux PLC, M.J.;Mallia,P.;Johnston,S.L.;Moffatt,M.F.;Cookson,W.O.C.;Maher,T.M. The role of the respiratory microbiome in idiopathic pulmonary fibrosis. Thorax 2013;**68 (Suppl 3)**:A22
25. Han MKE-D, Y.; Zhou, Y.; Tayob, N.; Murray,S.; Flaherty, K.R.; Huffnagle,G.B.; Martinez, F.J.;. The IPF Microbiome: Analysis from the COMET study. Am J Respir Crit Care Med 2013;**187**:A3769
26. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. N Engl J Med 1996;**335**(1):16-20
27. Zycinska K, Wardyn KA, Zielonka TM, Krupa R, Lukas W. Co-trimoxazole and prevention of relapses of PR3-ANCA positive vasculitis with pulmonary involvement. Eur J Med Res 2009;**14 Suppl 4**:265-7
28. Harvath L, Yancey KB, Katz SI. Selective inhibition of human neutrophil chemotaxis to N-formyl-methionyl-leucyl-phenylalanine by sulfones. J Immunol 1986;**137**(4):1305-11
29. Suda T, Suzuki Y, Matsui T, et al. Dapsone suppresses human neutrophil superoxide production and elastase release in a calcium-dependent manner. Br J Dermatol 2005;**152**(5):887-95
30. Anderson R, Grabow G, Oosthuizen R, Theron A, Van Rensburg AJ. Effects of sulfamethoxazole and trimethoprim on human neutrophil and lymphocyte functions in vitro: in vivo effects of co-trimoxazole. Antimicrob Agents Chemother 1980;**17**(3):322-6
31. Siegel JP, Remington JS. Effect of antimicrobial agents on chemiluminescence of human polymorphonuclear leukocytes in response to phagocytosis. J Antimicrob Chemother 1982;**10**(6):505-15
32. Welch WD, Davis D, Thrupp LD. Effect of antimicrobial agents on human polymorphonuclear leukocyte microbicidal function. Antimicrob Agents Chemother 1981;**20**(1):15-20
33. Cantin AM, North SL, Fells GA, Hubbard RC, Crystal RG. Oxidant-mediated epithelial cell injury in idiopathic pulmonary fibrosis. J Clin Invest 1987;**79**(6):1665-73
34. Felton VM, Borok Z, Willis BC. N-acetylcysteine inhibits alveolar epithelial-mesenchymal transition. Am J Physiol Lung Cell Mol Physiol 2009;**297**(5):L805-12
35. Psathakis K, Mermigkis D, Papatheodorou G, et al. Exhaled markers of oxidative stress in idiopathic pulmonary fibrosis. Eur J Clin Invest 2006;**36**(5):362-7
36. Behr J, Maier K, Krombach F, Adelmann-Grill BC. Pathogenetic significance of reactive oxygen species in diffuse fibrosing alveolitis. Am Rev Respir Dis 1991;**144**(1):146-50
37. Crystal RG, Bitterman PB, Rennard SI, Hance AJ, Keogh BA. Interstitial lung diseases of unknown cause. Disorders characterized by chronic inflammation of the lower respiratory tract (first of two parts). N Engl J Med 1984;**310**(3):154-66
38. Beeh KM, Beier J, Kornmann O, Buhl R. Neutrophilic inflammation in induced sputum of patients with idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 2003;**20**(2):138-43
39. Kinder BW, Brown KK, Schwarz MI, Ix JH, Kervitsky A, King TE, Jr. Baseline BAL neutrophilia predicts early mortality in idiopathic pulmonary fibrosis. Chest 2008;**133**(1):226-32
40. Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008;**63 Suppl 5**:v1-58
41. King TE, Jr., Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008;**177**(1):75-81
42. Chan TY. Co-trimoxazole-induced severe haemolysis: the experience of a large general hospital in Hong Kong. Pharmacoepidemiol Drug Saf 1997;**6**(2):89-92
43. Lee SH, Shim HS, Cho SH, et al. Prognostic factors for idiopathic pulmonary fibrosis: clinical, physiologic, pathologic, and molecular aspects. Sarcoidosis Vasc Diffuse Lung Dis 2011;**28**(2):102-12
44. Rosas IO, Richards TJ, Konishi K, et al. MMP1 and MMP7 as potential peripheral blood biomarkers in idiopathic pulmonary fibrosis. PLoS medicine 2008;**5**(4):e93

45. Collard HR, Calfee CS, Wolters PJ, et al. Plasma biomarker profiles in acute exacerbation of idiopathic pulmonary fibrosis. American journal of physiology. Lung cellular and molecular physiology 2010;**299**(1):L3-7
46. Strumpf IJ, Feld MK, Cornelius MJ, Keogh BA, Crystal RG. Safety of fiberoptic bronchoalveolar lavage in evaluation of interstitial lung disease. Chest 1981;**80**(3):268-71
47. British Thoracic Society guidelines on diagnostic flexible bronchoscopy. Thorax 2013;**68 Suppl 1**:i1-43