TIPAL

The effectiveness and risks of **T**reating people with **I**diopathic **P**ulmonary fibrosis with the **A**ddition of **L**ansoprazole (TIPAL): a randomised placebo-controlled multi-centre clinical trial

Version	2.0
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Sponsor	Norfolk and Norwich University Hospitals NHS Foundation Trust
Trial registration	ISRCTN13526307
CTA #	2020-000041-14
NRES #	20/EE/0043

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1 Administrative information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol template Version 4. It describes the TIPAL trial, sponsored by the Norfolk and Norwich University Hospitals NHS Foundation Trust and co-ordinated by NCTU.

It provides information about procedures for entering participants 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. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at NCTU.

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) 2012 Statement for protocols of clinical trials(1) The SPIRIT Statement Explanation and Elaboration document(2) can be referred to, or a member of NCTU Protocol Review Committee can be contacted for further detail about specific items.

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 2018 and General Data Protection Regulation (GDPR) 2018, and the UK Policy Framework for Health and Social Care Research, the European Directive 2001/20/EC (where applicable) and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and NCTU.

Participating sites will inform NCTU 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). 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

Norfolk and Norwich University Hospitals NHS Foundation Trust is the trial sponsor and has delegated responsibility for the overall management of the TIPAL trial to the Chief Investigator (CI) and NCTU. Queries relating to sponsorship of this trial should be addressed to the CI or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	EudraCT number: 2020-000041-14
Date of Registration in Primary Registry	03/01/2020
Secondary Identifying Numbers	ISRCTN number: ISRCTN13526307 IRAS number: 269050
Source of Monetary or Material Support	National Institute for Health Research Health Technology Assessment (HTA) Project: NIHR127479
Sponsor	Norfolk and Norwich University Hospitals NHS Foundation Trust
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Contact for Scientific Queries	Professor Andrew M Wilson Professor of Respiratory Medicine Floor 2, Bob Champion Research and Education Building Rosalind Franklin Road University of East Anglia Norwich Research Park Norwich, Norfolk NR4 7TJ A.M.Wilson@uea.ac.uk
Short Title or Acronym	TIPAL: Treating people with Idiopathic Pulmonary fibrosis with the Addition of Lansoprazole
Scientific Title	The effectiveness and risks of Treating people with Idiopathic Pulmonary fibrosis with the Addition of Lansoprazole (TIPAL): a randomised placebo-controlled multi-centre clinical trial
Countries of Recruitment	United Kingdom
Health Condition(s) or Problem(s) Studied	Idiopathic Pulmonary Fibrosis
Intervention(s)	Patients will be randomised on a 1:1 basis to receive either; ACTIVE ARM: Oral lansoprazole 30 mg (as 2 x 15mg capsules) twice daily, 12 hours apart, for 12 months

	or CONTROL ARM: Matched placebo (2 capsules) twice daily, 12 hours apart, for 12 months Trial drug is to be taken at least 30 minutes before food. Dose may be reduced to one capsule twice daily in those developing adverse reactions (see section 6.4.1.4)
Key Inclusion and Exclusion 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. 2018;198:e44-e68 (50)). 3. Patients may be receiving licensed anti-fibrotic medication (for at least 4 weeks prior to randomisation with no planned amendments for at least 4 weeks post-randomisation). 4. Able to provide informed consent. Additional Inclusion Criteria for cough count sub-study: 1. Pre-existing diagnosis of persistent cough (defined as a troublesome cough for more than 8 weeks prior to enrolment). **Exclusion Criteria:** 1. Patients unable to comply with study assessments including the ability to complete reliable spirometry assessments. 2. Concomitant use of a proton pump inhibitor (PPI) or prokinetic drugs (cisapride, domperidone, metoclopramide, erthryomycin, pruclopride etc.) within 2 weeks prior to randomisation. 3. Patients with a self-reported respiratory tract infection within 4 weeks of screening (defined as two or more of: increased cough, sputum or breathlessness and requiring antimicrobial therapy) 4. Significant co-existing respiratory disease (defined as respiratory condition that exhibits a clinically relevant effect on respiratory symptoms and disease progression as determined by the Principal Investigator (PI). The presence of traction bronchiectasis is permitted. 5. Patients with FEV1/FVC<0.7. 6. Significant medical, surgical or psychiatric disease that in the opinion of the patient's attending

	physician would affect subject safety or influence the study outcomes including liver failure (e.g. serum transaminase > 2 x upper limit of normal, Bilirubin > 1.5 upper limit of normal (unless the patient has Gilbert's Syndrome) and chronic kidney disease (CKD) greater than stage 3, erosive oesophagitis, Barrett's oesophagus or any condition requiring lifelong proton pump inhibitor use. 7. Known allergy to proton pump inhibitors or the contents of placebo. 8. Concomitant use of atazanavir, ketoconazole, itraconazole, tacrolimus, methotrexate, fluvoxamine (see section 6.4.5). 9. Females who are of childbearing potential or lactating. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. 10. Receipt of another investigational drug or biological agent associated with another clinical trial within the 4 weeks prior to TIPAL study enrolment or 5 times the drug half-life, whichever is the longer. 11. Receiving long term oxygen therapy. 12. Patients with hypomagnesemia (defined as magnesium ≤0.6 mmol/L). Potential patients receiving PPIs may undergo a washout period of 2 weeks if clinically acceptable with randomisation into the study to follow if asymptomatic at the end of this period. In the event a patient fails screening due to presentation with magnesium deficiency or self-reported respiratory tract infection within four weeks of screening, they may be re-screened once magnesium levels have returned to ≥0.7mmol/L and/or four weeks have elapsed since respiratory tract infection symptom onset.
Study Type	This study is an interventional clinical trial of an investigational medicinal product: a phase III, randomised, placebo-controlled, two arm parallel group, double-blind, multicentre clinical trial. Randomisation will be generated by a secure web-based system on a 1:1 basis with minimisation for recruiting site, baseline IPF treatment, reflux and cough.

Date of First Enrolment	October2020
Target Sample Size	298 participants (149 per group); 160 (80 per group) of whom will be recruited in to the cough count sub-study.
Primary Outcome(s)	Absolute change in percentage predicted (%) forced vital capacity (FVC) at 12 months post-randomisation of lansoprazole versus placebo.
Key Secondary Outcomes	The following secondary outcomes will be assessed at the timepoints specified: **At 3 months post-randomisation:** • cough frequency measured using a VitaloJAK cough monitor, over a 24 hour period **At 3, 6, 9 and 12 months post-randomisation:** • cough score measured using a 100mm visual analogue scale (VAS) • cough related quality of life measured by the Leicester cough questionnaire (LCQ) • breathlessness measured by the Medical Research Council (MRC) Dyspnoea scale • disease specific quality of life measured using the King's Brief Interstitial Lung Disease (K-BILD) questionnaire • health related quality of life (HR-QoL) measured using the EQ5D-5L questionnaire (quality adjusted life years will be estimated) • adverse events with particular relevance to respiratory tract infection and pneumonia, *Clostridium difficile* infection and hypomagnesaemia **At 3, 6 and 12 months post-randomisation:** • total lung diffusing capacity of carbon monoxide (DLCO) measured (corrected for haemoglobin) where possible • Laboratory assessment of FVC and FEV1 where possible **At 3 and 12 months post-randomisation:** • sleep quality measured by the short Pittsburgh Sleep Quality Index (PSQI)

	• reflux characteristics measured by the DeMeester score **At 12 months post-randomisation:** • participant acceptability measured by a study-specific questionnaire • risk of sleep apnoea measured by the STOP-bang questionnaire • progression free survival (with progression defined as time from date of randomisation to week of all-cause death, lung transplant, a 10% absolute reduction in FVC % predicted from baseline measured by weekly domiciliary spirometry) • hospital-free survival defined as death (all-causes) or first non-elective (all-cause) hospital admission. • Respiratory related hospital free survival **Over the course of 12 months:** • the decline and rate of decline in absolute %FVC based on %FVC measured weekly

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the Trial Master File (TMF) for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Professor Andrew Wilson	UEA	CI
Dr Nazia Chaudhuri	Manchester University NHS Foundation Trust	Co-applicant
Dr Allan Clark	UEA	Senior Medical Statistician
Dr Ian Forrest	The Newcastle upon Tyne Hospitals NHS Foundation Trust	Co-applicant
Matthew Hammond	NCTU	Deputy Director of NCTU
Megan Jones	NCTU	Trial Manager
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Dr Helen Parfrey	Royal Papworth Hospital NHS Foundation Trust	Co-applicant
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Mr Shajahan Wahed	The Newcastle upon Tyne Hospitals NHS Foundation Trust	Co-applicant
Dr Chris Ward	Newcastle University	Co-applicant

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
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Michael Sheridan	NNUH	Sponsor: Research Grants Coordinator
Ania Spurdens	NNUH	Sponsor: Research Study and Recruitment Facilitator
Donna White	NIHR HTA	Funder: Research Manager

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
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Antony Colles	NCTU	Senior Data Programmer
Matthew Hammond	NCTU	Deputy Director of NCTU
Megan Jones	NCTU	Trial Manager
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1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
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Dr Chris Ward	Newcastle University	Co-investigator
Dr Estelle Payerne	NCTU	SWAT

1.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Professor Ann Millar	Retired/University of Bristol	Independent Chair
Professor Adam Hill	NHS Lothian/University of Edinburgh	Independent Member
Dr Katherine O'Reilly	Mater Misericordiae University Hospital	Independent Member
Dr Oleg Blyuss	University of Hertfordshire	Independent Statistician
George Crowe	N/A	Patient and Public Involvement Representative
Martin Ruddock	N/A	Patient and Public Involvement Representative

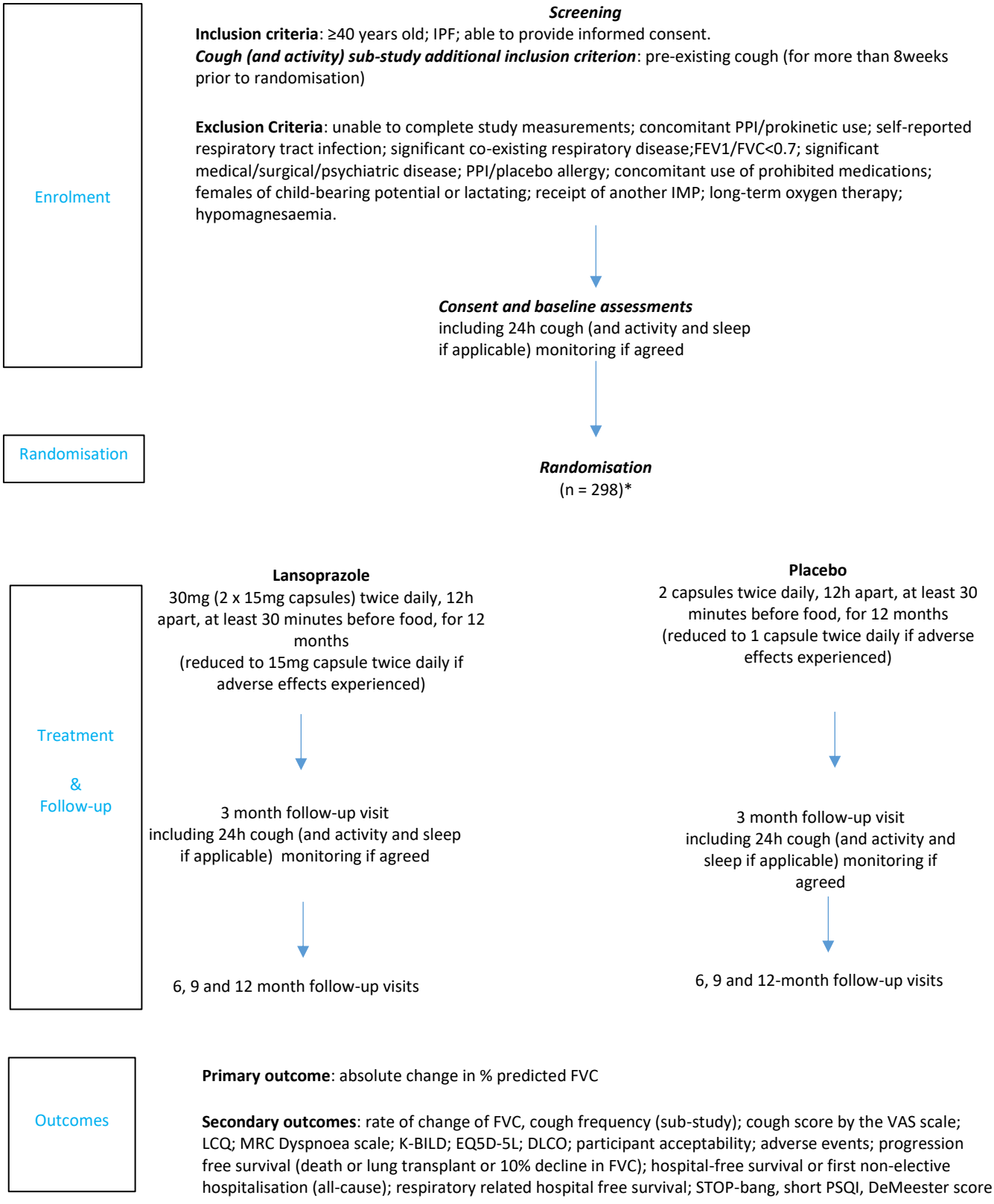
1.4.6 Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Dr Nik Hirani	University of Edinburgh	Independent Chair

Professor Sarah Pett	Medical Research Council Clinical Trials Unit at University College London	Independent Member
Dr Mona Kanaan	University of York	Independent Statistician

2 Trial Diagram

Figure 1: TIPAL trial diagram



*160 patients (80 per group for cough (and activity if applicable) sub-study
Full eligibility criteria details listed in section 6.3.1, outcomes described in section 6.5 and participant assessments outlined in section 6.6.1.

3 Abbreviations

AE	Adverse Event
APF	Action for Pulmonary Fibrosis
AR	Adverse Reaction
ARTP	Association for Respiratory Technology and Physiology
ATS	American Thoracic Society
BTS	British Thoracic Society
CACE	Compliance-Adjusted Causal Effect
CAP	Community acquired pneumonia
CDAD	*Clostridium difficile* associated diarrhoea
CI	Chief Investigator
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	Diffusing capacity of Carbon Monoxide
DMC	Data Management Committee (aka IDMC)
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EME-TIPAC	The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary fibrosis with the Addition of Co-trimoxazole
ERS	European Respiratory Society
EU	European Union
FBC	Full Blood Count
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOR	Gastro-oesophageal reflux
GORD	Gastro-oesophageal reflux disease
GP	General Practitioner
H2A	Histamine-2 receptor antagonists
HRA	Health Research Authority
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee (aka DMC)
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
INR	International normalised ratio
IPF	Idiopathic Pulmonary Fibrosis
ISF	Investigator Site File
ITT	Intention to Treat
ISRCTN	International Standard Randomised Clinical Trial Number
K-BILD	King's Brief Interstitial Lung Disease questionnaire
LCQ	Leicester Cough questionnaire
LFTs	Liver Function Tests
MDT	Multi-Disciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
NCTU	Norwich Clinical Trials Unit

NICE	National Institute for health and Care Excellence
NIHR	National Institute of Health Research
NNUH	Norfolk and Norwich University Hospitals NHS Foundation Trust
PI	Principal Investigator
PID	Participant Identification Number
PIS	Participant Information Sheet
PPI	Proton Pump Inhibitor
PPIPF	Proton Pump Inhibitors in idiopathic Pulmonary Fibrosis
PSQI	Pittsburgh Sleep Quality Index
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study Within A Trial
TIPAC	Treating Idiopathic Pulmonary fibrosis with the Addition of Co-trimoxazole
TIPAL	Treating Idiopathic Pulmonary fibrosis with the Addition of Lansoprazole
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UEA	University of East Anglia
ULN	Upper Limit of Normal
U&Es	Urea and Electrolytes
VAS	Visual Analogue Scale

4 Glossary

None.

5 Introduction

5.1 Background and Rationale

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic interstitial lung disease (ILD) of unknown cause with a poor prognosis and limited treatment options. It is progressive and usually fatal with a 5-year survival of 20-40%(3). More people will die each year from IPF than from ovarian cancer, leukaemia or mesothelioma(4). People with this condition experience progressive breathlessness and a socially isolating cough, with cough being particularly difficult to treat. They frequently have comorbid disease, gastro-oesophageal reflex disease (GORD) being one of the most common.

Reflux disease and anti-reflux therapy in IPF: clear associations

The cause of IPF is unknown, however, there are well-accepted aetiological factors including genetic variants and environmental exposures, for example smoking and aspiration of gastric fluid(5). IPF itself may increase gastro-oesophageal reflux (GOR) by reducing intra-thoracic pressure or because of increased oesophageal traction(6). Indeed nearly 90% of people with IPF have GOR(7), with a correlation between radiological evidence of lung fibrosis and oesophageal reflux episodes(8). Despite this, only half of individuals have classic reflux symptoms(7).

Case series and secondary analysis of randomised clinical trials (RCTs), suggest that anti-reflux therapy slows disease progression. In a pooled analysis of 242 individuals taken from the placebo arms of three trials, anti-acid therapy resulted in a statistically and clinically significant difference in absolute forced vital capacity (FVC) decline over a 30-month period(9). This amounted to a 50% reduction in FVC decline. However these findings were not replicated in a post-hoc analysis of data from individuals with IPF and FVC > 50% predicted, randomised to the placebo(10) arm of the CAPACITY studies, possibly due to the unadjusted nature of the analysis(11).

Two systematic reviews have reported the effect of anti-acid therapy on mortality. Tran and Suissa(12) examined all-cause mortality and reported an overall reduction with anti-acid therapy but argued that the signal for this difference mostly came from studies subject to possible immortal time bias. Fidler et al(11) found no effect on all-cause mortality but reported a reduction of IPF-related mortality.

PPIs are the cornerstone of anti-reflux therapy

Proton Pump Inhibitors (PPIs) are the first-line anti-acid treatments for people with reflux disease according to current National Institute for Health and Care Excellence (NICE) guidelines (www.nice.org.uk/CG184). Histamine-2 receptor antagonists (H2A), previously first-line treatment, have been superseded by PPIs given the clear evidence of greater acid suppression and symptomatic control(13). Thus, H2A are only now offered to those with an inadequate response to PPIs. Prokinetics are not recommended by NICE guidelines, cannot be used for long-term therapy due to concerns about adverse effects and do not improve symptomatic or endoscopic response in GORD(14). Laparoscopic fundoplication results in better symptom control but worse side effects than PPIs(15), but this intervention can only be advocated for highly selected individuals with IPF. Lifestyle changes are recommended by guidelines and may improve symptom burden(16). A review found evidence to support sleeping head-up and weight loss improved pH profiles and symptoms(17). Antacids and raft

alginates also have a limited role in treating dyspepsia, with alginates being better than antacids but less effective than PPIs or H2A(18).

Overall, nearly all of the evidence about anti-reflux therapy in IPF comes from people receiving PPIs. All of the individuals in the initial case series were taking PPIs and more than 90% of individuals in the secondary analysis of clinical trials were receiving PPIs. PPIs have anti-inflammatory, anti-oxidant and anti-fibrotic properties demonstrated *in vitro*(19) and *in vivo*(20). Thus, there are plausible biological mechanisms by which they may reduce disease progression in addition to their anti-acid effects(21). A small randomised control trial of a PPI in people with IPF (PPIPF)(22) showed that a definitive large-scale trial was feasible. As expected, the main reason for exclusion was due to existing PPI therapy, however 25 out of 59 people taking PPIs were eligible for a trial of withholding therapy for two weeks after which 16 (64%) did not have a return of symptoms and were able to successfully enter into the trial. PPIs were well tolerated in IPF with slightly increased lower respiratory tract infections in the active arm. Invasive assessment of GORD was not considered feasible but there was a suggesting of a meaningful improvement in objective cough scores. GORD may influence sleep quality in people with IPF due to nocturnal coughing, which was shown to be improved in the PPIPF trial(22) indeed GORD, IPF, coughing and obstructive sleep apnoea may be interrelated(23).

Of the five licensed PPIs in the UK, omeprazole and esomeprazole induce cytochrome enzymes potentially resulting in reduced efficacy of the anti-fibrotic drug pirfenidone (www.medicines.org.uk/emc/medicine/29932). The acid suppression potency(24) and symptom relief of the remaining PPIs is similar(25), however lansoprazole is the cheapest available PPI and the one with which UK physicians are most familiar.

Non-erosive oesophagitis occurs at a higher pH than erosive gastritis and therefore higher doses of PPIs are often required to increase the pH to a degree that will treat non-reflux symptoms such as cough(26). Lansoprazole 30mg twice per day results in significantly greater acid suppression and for longer duration than lower doses(27), with a pH greater than 4 occurring 75% of the time with 30mg twice daily compared to 60% of the time with 30mg once daily or 15 mg twice daily. However very high doses do not produce greater acid suppression(27). A dose of 30mg twice daily (with a dose step-down option if adverse effects emerge), will minimise resistant reflux disease although may result in slightly higher rates of diarrhoea (5.0% compared to 3.7% for 30mg daily)(28).

PPI: potential adverse effects Long-term PPI therapy may result in significant adverse effects. A systematic review and meta-analysis of 26 studies evaluating six million people showed that PPI therapy increases the risk of community-acquired pneumonia (CAP), including CAP requiring hospitalisation(29), by 50%. This is in keeping with the suggestion of a higher incidence of pneumonia with PPI therapy in patients with IPF randomised to the placebo arm of the CAPACITY studies(38), albeit in those with more severe disease(30). Pneumonia is common in people with IPF(31) and a frequent cause of death(32). Alkaline stomach pH is thought to permit bacterial colonisation, which can be aspirated – a risk that may be increased in IPF-related GOR and micro-aspiration. Osteoporosis is also increased by 25-50% with PPI treatment(33). *Clostridium difficile*-associated diarrhoea (CDAD) is increased with PPI use and outcomes for CDAD are worse for those receiving PPIs(34).

Primary outcome data collection

FVC is regarded as a clinically meaningful endpoint for phase 3 clinical trials(35) and the most appropriate option given that mortality is impractical(36) (37). FVC has been utilised as the primary endpoint in nearly all published late phase clinical trials in IPF, including those of pirfenidone and nintedanib, which were used for licensing purposes. FVC has been accepted by the Food and Drug Administration (FDA) as an appropriate endpoint for licensing of medication(38). The change in FVC over time has been repeatedly shown to be highly predictive of mortality(39) and is a component of prognostic algorithms. Furthermore, as it is captured at least annually by all centres entering data onto the British Thoracic Society (BTS) ILD Registry (www.brit-thoracic.org.uk/standards-of-care/lung-disease-registries/bts-ild-registry/), long-term follow-up using FVC can be undertaken at minimal inconvenience to patients and the service.

Spirometry is considered to be an aerosol generating procedure (https://www.artp.org.uk/News/artp-guidance-respiratory-function-testing-and-sleep-services-during-endemic-covid-19) and as a result provision for undertaking laboratory FVC measurements is limited. For this reason, along with the technological advances in spirometers and internet network connections, home spirometry is increasingly used as a clinical method of monitoring chronic respiratory disease. Home spirometry has been shown to be a good predictor of mortality(40) and has good adherence at least up to 24 weeks(41). Home spirometry has been repeatedly shown to have good correlation with laboratory spirometry(40, 41) with correlation coefficients greater than 0.9. It has been utilised in as an endpoint in a clinical trial of unclassifiable fibrotic interstitial lung disease but linear regression modelling was not possible (42).

5.1.1 Explanation for choice of comparators

Lansoprazole will be compared with matched placebo as this is the most robust way to determine the efficacy and adverse effects of lansoprazole. All patients involved in the trial will continue to receive usual care (defined in section 6.4.5).

Treatment allocation is double-blinded to reduce potential bias in reporting of the primary outcome and patient reported secondary outcomes.

5.2 Objectives

The primary research hypothesis is that participants treated with lansoprazole will have smaller absolute decline in percentage predicted (%) FVC at 12 months post-randomisation versus participants treated with placebo.

The secondary research hypotheses are that participants treated with lansoprazole will:

- cough fewer times over a 24h period at 3 months than participants treated with placebo
- have a lower cough score assessed by the VAS score than participants treated with placebo at each study time point following baseline
- have a better cough-related quality of life as measured by the LCQ than participants treated with placebo at each study time point following baseline
- experience less breathlessness indicated by the MRC Dyspnoea scale than participants treated with placebo at each study time point following baseline

- have a better disease specific quality of life as measured by the K-BILD than participants treated with placebo at each study time point following baseline
- have a higher DLCO than participants treated with placebo at each study time point following baseline
- regard their trial treatment as acceptable at 12 months
- experience fewer all-cause and respiratory-related hospitalisations and deaths as a group than the placebo treatment group at 12 months
- experience longer progression free survival than participants treated with placebo
- be at a lower risk of sleep apnoea according to the STOP-bang questionnaire at 12 months than participants treated with placebo
- have a better sleep quality score indicated by the short PSQI at 3 and 12 months than participants treated with placebo
- have a lower DeMeester score at 3 and12 months than participants treated with placebo
- have a smaller absolute rate of decline in FVC over time than participants treated with placebo

5.3 Trial Design

The study is a Phase III double blind, parallel group, 1:1 randomised, placebo controlled, multi-centre, clinical superiority trial of oral lansoprazole versus placebo in 298 participants with IPF diagnosed by multi-disciplinary team (MDT) meeting consensus, according to international criteria for IPF. Outcomes will be assessed during a treatment period of 12 months. The primary endpoint is absolute change in % predicted FVC measured between baseline and 12 months post-randomisation of lansoprazole versus placebo. FVC will be measured on a weekly basis during the trial by domiciliary spirometry. Randomisation will be performed centrally according to a computer-generated randomisation code by secure automated e-mail from NCTU to central research pharmacists only. Minimisation factors are: recruiting site, baseline anti-fibrotic therapy, presence of reflux and presence of cough.

A subgroup of 160 participants (80 per group) will be recruited in to the cough count sub-study.

5.3.1 Pilot Phase

This study includes an internal pilot phase during which recruitment will be closely monitored by all relevant parties and oversight committees to ensure recruitment of the planned sample size is feasible, safe and ethical.

Progression will be assessed constantly throughout the study according to a traffic light system, with green flagging if the study is progressing above target, red flagging if the study is not likely to deliver and amber flagging if in between. Observed total recruitment will be assessed against expected total recruitment to assign flags. A red flag is indicated where the observed recruitment total is less than 50% of the expected recruitment total for the relative study timepoint.

Actions to be taken according to the progression flagging status;

- Green flagging – study and recruitment to continue as planned
- Amber flagging – results in increased recruitment of sites and discussion and monitoring of existing sites regarding recruitment and best practice approached

- Red flagging – three consecutive red flag months will trigger discussion with the Data Monitoring Committee (DMC), Trial Steering Committee (TSC) and Sponsor regarding feasibility of continuing recruitment

The Study Within A Trial (SWAT) will be abandoned with provisional findings incorporated into the recruitment strategy at all sites if there is amber flagging at 24 months or red flagging at 18 months.

The pilot phase will commence from the date the first recruiting site is activated to recruitment. At the end of the pilot phase a decision will be made by the funder, in consultation with the TSC and DMC, regarding progression to completion of the trial as intended. Recruitment will continue until this decision has been reached. All participants recruited during the pilot phase will be included in the further study analyses.

There are no planned interim efficacy analyses.

6 Methods

6.1 Site Selection

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

6.1.1 Study Setting

The study will be conducted primarily in secondary and tertiary care hospitals within the United Kingdom. Sites will be specialist ILD centres, meet the specifications required for specialist ILD centre status or work in association with specialist centres. Due to the restrictions in face-to-face clinical and research consultations, resulting from the COVID-19 pandemic, outcomes will be collected remotely without the requirement of hospital/research centre attendance along with opportunistic capture of routine clinical outcome assessments.

6.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of this protocol and the Summary of Product Characteristics (SPC).

To participate in the TIPAL trial, investigators and trial sites must fulfil a set of criteria, agreed by the TIPAL Trial Management Group (TMG), as defined below. In exceptional circumstances, a site may be excluded from some aspects of the study if they do not meet the criteria below following approval from the CI.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator (PI) responsibility
- Suitably trained staff are available to recruit participants, undertake/observe study assessments and measurements, enter data and collect and store samples
- Site is included on the BTS IPF and Sarcoidosis registry or willing to join registry prior to activation
- The site has a suitable potential patient population to adequately recruit participants from

Sites are not required to have access to a pharmacy able to store, prepare and dispense Investigational Medicinal Product (IMP) as these processes will be managed through a central pharmacy (see section 6.4.3).

In addition, selected sites will be invited to participate in the TIPAL cough count sub-study and will approach and consent eligible patients accordingly.

Trial sites meeting eligibility criteria will be issued with a TIPAL Investigator Site File (ISF) and a pack of documentation needed by the Research and Development (R&D) Department of their Trust to enable the Trust to provide confirmation of capacity and capability to undertake the study.

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign an investigator statement to comply with the trial protocol (confirming their specific role and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial (see section 12)). This includes confirmation of appropriate qualifications, familiarity with the appropriate use of any investigational products, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

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. 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.

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 (PIs). Trial staff at NCTU will perform this task.

On receipt of the signed investigator statement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site initiation. Sites will not be permitted to recruit any patients until a letter for activation has been issued. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor, Health Research Authority (HRA) and, by the regulatory authority (as appropriate), and which was given

favourable opinion by the Research Ethics Committee (REC). 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 Trial Manager.

6.3 Participants

6.3.1 Eligibility Criteria

6.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of randomisation. 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 participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants 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.

In the event a patient fails screening due to presentation with magnesium deficiency or self-reported respiratory tract infection within four weeks of screening, they may be re-screened once magnesium levels have returned ≥0.7mmol/L and/or four weeks have elapsed since respiratory tract infection symptom onset. Participants are permitted to repeat baseline FVC measurements upon receipt of the domiciliary spirometer to familiarise themselves on use of the equipment. Baseline FVC measurements should be attempted for a period up to a maximum of 14 days upon which, a decision as to whether to proceed to trial enrolment will be made by the local PI in collaboration with the CI and patient where appropriate, if clinically consistent results have been challenging to obtain.

6.3.1.2 Participant 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. 2018;198:e44-e68 (50)).
3. Patients may be receiving licensed anti-fibrotic medication (for at least 4 weeks prior to randomisation with no planned amendments for at least 4 weeks post-randomisation).
4. Able to provide informed consent.

<u>Additional Inclusion Criteria for cough count sub-study:</u>

1. Pre-existing diagnosis of persistent cough (defined as troublesome for more than 8 weeks prior to study enrolment).

6.3.1.3 Participant Exclusion Criteria

1. Patients unable to comply with study assessments including the ability to complete reliable spirometry assessments.
2. Concomitant use of a proton pump inhibitor (PPI) or prokinetic drugs (cisapride, domperidone, metoclopramide, erthryomycin, pruclopride etc.) within 2 weeks prior to randomisation.

3. Patients with a self-reported respiratory tract infection within 4 weeks of screening (defined as two or more of: increased cough, sputum or breathlessness and requiring antimicrobial therapy).
4. 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 PI). The presence of traction bronchiectasis is permitted.
5. Patients with an FEV1/FVC<0.7.
6. Significant medical, surgical or psychiatric disease that in the opinion of the patient's attending physician would affect subject safety or influence the study outcomes including liver failure (e.g. serum transaminase > 2 x upper limit of normal (ULN), Bilirubin > 1.5 x ULN (unless the patient has Gilbert's Syndrome) and chronic kidney disease (CKD) greater than stage 3 , erosive oesophagitis, Barrett's oesophagus or any condition requiring lifelong proton pump inhibitor use.
7. Known allergy to proton pump inhibitors or the contents of placebo.
8. Concomitant use of atazanavir, ketoconazole, itraconazole, tacrolimus, methotrexate, fluvoxamine (see section 6.4.5).
9. Females who are of childbearing potential or lactating. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
10. Receipt of another investigational drug or biological agent associated with another clinical trial within the 4 weeks prior to TIPAL study enrolment or 5 times the drug half-life, whichever is the longer.
11. Receiving long-term oxygen therapy.
12. Patients with hypomagnesemia (defined as magnesium ≤0.6 mmol/L).

Patients receiving PPIs prior to study participation invitation, may undergo a 2 week washout period, if clinically acceptable, with randomisation into the study if they remain asymptomatic at the end of this period. The patient's GP should be contacted, via the study GP letter, following the informed consent process in order to notify them of the intention for their patient to complete the washout period.

FEV1/FVC ratios should be assessed at screening from the most recent spirometry assessments taken in the clinic recorded in patient notes.

Investigators are encouraged to contact the TIPAL CI, via the NCTU trial team, for guidance in assessing eligibility in relation to exclusion criterion **six** prior to approaching the patient about the trial if required.

Magnesium deficiency was defined based on 0.7 - 1.0mmol/L being regarded as a typical normal range(49).

6.3.1.5 Co-enrolment Guidance

Concurrent participation in clinical trials of investigational medical products is not permitted. However, participants may be entered into other observational studies given prior agreement from the CI of both studies.

6.3.1.6 Screening Procedures and Pre-randomisation Investigations

Written informed consent to enter and be randomised into the trial must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial and

BEFORE any trial-specific procedures. 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 part of usual standard of care.

6.4 Interventions

6.4.1 Active treatment arm

6.4.1.1 Products

Oral lansoprazole (generic).

6.4.1.2 Treatment Schedule

Participants will be asked to take 30mg (as 2 x 15mg capsules) twice daily, 12 hours apart, for 12 months. IMP should be taken at least 30 minutes before food.

6.4.1.3 Dispensing

Participants will have investigational medicinal product (IMP) dispensed 6 monthly. The IMP will be supplied in packages providing **one month's supply**. IMP will be shipped to the participant's home address by the study's central pharmacy. A dosing card will be dispensed with the IMP stating the required treatment schedule.

6.4.1.4 Dose Modifications, Interruptions and Discontinuations

Treatment should be reduced to 15mg (as 1 x 15mg capsule) twice daily, at least 30 minutes before food, in those confirmed or suspected of developing adverse reactions as outlined below:

- Respiratory tract infection and pneumonia
- *Clostridium difficile* infection
- Hypomagnesaemia defined as magnesium levels of ≤0.6mmol/L

Trial treatment dose may be reduced to 15mg (1 x 15mg capsule) due to patient and/or clinician discretion.

Site staff should ensure that all reports of these adverse effects are recorded on the electronic Case Report Form (eCRF) as completely as possible.

Participants will be administered a new dosing card containing details of the reduced treatment schedule; the superseded dosing card should be returned to site, by freepost/courier or in person, at the next visit following dose reduction.

If a participant 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. Participants must not take a double dose to make up for a forgotten dose. Interruptions should be avoided where possible, any reported should be recorded on the eCRF.

6.4.2 Placebo Arm

6.4.2.1 Products

Placebo (manufactured to appear identical to IMP).

6.4.2.2 Treatment Schedule

Participants will be asked to take 2 capsules twice daily, 12 hours apart, for 12 months. Treatment should be taken at least 30 minutes before food.

6.4.2.3 Dispensing

The TIPAL trial is a double-blind study and so dispensing for the placebo arm will be managed identically to the active arm (see section 6.4.1.3).

6.4.2.4 Dose Modifications, Interruptions and Discontinuations

Treatment may be reduced to 1 capsule twice daily, at least 30 minutes before food, in those developing adverse reactions (see section 6.4.1.4) at the discretion of the PI or by participant choice. The reason for dose modification will be documented in the eCRF. Participants will be administered a new dosing card containing details of the reduced treatment schedule; the superseded dosing card should be returned to site, by freepost/courier or in person, at the next visit following dose reduction.

If a participant 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. Participants must not take a double dose to make up for a forgotten dose. Interruptions should be avoided where possible, any reported should be recorded on the eCRF.

6.4.3 Accountability

The central pharmacy will be responsible for drug accountability for all sites, this includes records of drug and placebo received at the pharmacy, dispensed to participants and unused drug and will ensure batch recall is possible in event of it being necessary. The central pharmacy are also responsible for ensuring IMP is handled and stored appropriately, dispensed accurately and for shipping IMP to each participant's home address on a 6 monthly basis during trial participation (upon receipt of an appropriately signed prescription).

IMP will be returned to the central pharmacy for destruction.

6.4.4 Compliance and Adherence

Compliance to study treatment, in the form of returned capsule counts, will be monitored as part of drug accountability at relevant visits as outlined in section 6.6.

6.4.5 Concomitant Care

Standard Care

All participants will receive treatment as usual for their IPF regardless of randomisation into this trial. Standard care will be as defined by NICE guidelines (www.nice.org.uk/CG163) including anti-fibrotic therapy, pulmonary rehabilitation, oxygen, transplant referral and palliative care input as appropriate. Comorbidities are identified and managed according to individual disease-specific guidelines. All participants (in the control and intervention arms) will be provided with the publicly available British Digestive Disorder Charity (CORE) patient information leaflet about heartburn and reflux at entry into the study. This provides information about the causes, investigations and treatment for reflux including lifestyle changes. Dyspepsia will be managed with lifestyle changes, reviewing the requirement for medications causing dyspepsia and treatment with antacids and alginates in both

groups as required at any time in the study. Participants still symptomatic with these treatments, or requiring PPIs for oesophagitis or duodenal ulcer, will be withdrawn from the study.

Concomitant medication

Patients receiving anti-fibrotic medication for their IPF must have been in receipt of the treatment for at least 4 weeks prior to randomisation and not have any planned amendments for at least 4 weeks post-randomisation. Use of antacids and raft alginates is also permitted.

All concomitant medication including over the counter and herbal remedies will be recorded at baseline with any changes during participation recorded.

Non-permitted medication

The following medications are not permitted due to interactions, described in the SPC, with lansoprazole as outlined below and thus patients are **excluded** from the study (see section 6.3.1.3):

- HIV protease inhibitors – e.g. atazanavir- due to significant reduction in bioavailability when co-administered with lansoprazole
- Ketoconazole and itraconazole – absorption is enhanced by the presence of gastric acid thus co-administration with lansoprazole may result in sub-therapeutic concentrations of these drugs
- Methotrexate – serum levels may be elevated and prolonged (including of its metabolite) when co-administered with lansoprazole
- Tacrolimus - increased plasma concentrations when co-administered with lansoprazole
- Fluvoxamine – increases plasma concentrations of lansoprazole significantly
- Prokinetics – due to potential to contaminate study results. Sites are therefore advised to review patient's concomitant medication and amend prescriptions for prokinetics (cisapride, domperidone, metoclopramide, erythromycin, pruclopride etc.) accordingly if trial participation is otherwise deemed safe and appropriate and the patient wishes to consent (see exclusion criteria 2).
  *N.B. Erythromycin **is** permitted for short-term antibiotic use only during the trial.*

Increased monitoring

Concomitant medication requiring increased monitoring:

- Warfarin – monitored for increase in international normalised ratio (INR) and prothrombin time.
- Digoxin – increased plasma levels when co-administered with lansoprazole
- Theophylline – reduced plasma concentrations when co-administered with lansoprazole

Sites are responsible for providing increased monitoring for participants receiving the above mentioned medication(s) and for any others the PI or sub-investigator deem appropriate. Results of additional monitoring procedures do not need to be recorded on the eCRF.

Additional guidance

Sucralfate and antacids may decrease the bioavailability of lansoprazole. Therefore lansoprazole should be taken at least 1 hour after taking these medicinal products.

6.4.6 Overdose of Trial Medication

The SPC for Lansoprazole states: "The effects of overdose on lansoprazole in humans are not known (although the acute toxicity is likely to be low) and, consequently, instruction for treatment cannot be given. However, daily doses of up to 180 mg of lansoprazole orally and up to 90 mg of lansoprazole intravenously have been administered in trials without significant undesirable effects."

Treatment is symptomatic and supportive care. Observe the patient for at least four hours and monitor Urea & Electrolytes (U&Es) and full blood count (FBC) in symptomatic cases. Lansoprazole is not significantly eliminated by haemodialysis. If necessary, gastric emptying, charcoal and symptomatic therapy is recommended.

6.4.7 Protocol Treatment Discontinuation

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

- 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
- Where patients are unable or unwilling to continue to undertake study measurements/activities, the decision as to whether the participant should continue with trial treatment and/or follow-up assessments will be at the discretion of the local PI and/or CI.

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. 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.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis.

6.5 Outcomes

6.5.1 Primary Outcome

The primary outcome will be disease progression as assessed by absolute change in % predicted forced vital capacity (FVC) at 12 months post-randomisation of lansoprazole versus placebo.

6.5.2 Secondary Outcomes

The following secondary outcomes will be assessed comparing lansoprazole to placebo:

Cough frequency:

- Measured using a VitaloJAK cough monitor over a 24 hour period at baseline and 3 months post-randomisation

- 160 patients (80 per group) will be included in this secondary outcome sub-study analysis

Cough Score, general Health Related and Disease Specific Quality of Life and Breathlessness:

Participants to complete the following questionnaires at baseline and 3, 6, 9 and 12 months post-randomisation to assess outcomes listed:

- Cough score using a 100mm VAS
- Cough related quality of life as indicated by the LCQ(43)
- Breathlessness measured by the Medical Research Council (MRC) Dyspnoea Scale(44)
- Disease specific quality of life measured using the K-BILD questionnaire(45)
- Health-related quality of life indicated by the EQ5D-5L questionnaire to estimate quality adjusted life years(46)

Lung Function:

- total DLCO (corrected for haemoglobin) will be measured at baseline and 3, 6 and 12 months post-randomisation where possible. (NB measurements will be taken regardless of whether measurements were taken at the previous timepoint, i.e. DLCO may be measured at baseline and 12 months only)
- FVC and FEV1 will be measured at baseline and weekly post-randomisation at home and obtained from laboratory assessments at baseline 3, 6 and 12 months post-randomisation where possible
- the decline and rate of decline in absolute %FVC based on %FVC measured weekly from baseline to 12 months post-randomisation

Acceptability:

- measured by a study-specific non-validated questionnaire completed at 12 months post-randomisation

Sleep:

- participant risk of sleep apnoea will be estimated by the STOP-bang questionnaire at 12 months post-randomisation
- participant sleep quality will be assessed using the short PSQI at baseline and 3 and 12 months post-randomisation

Reflux characteristics:

- a DeMeester score will be assessed at baseline and 3 and 12 months post-randomisation

Safety, Hospitalisation and Death:

- adverse events with particular relevance to confirmed or suspected diagnoses of respiratory tract infection and pneumonia, *Clostridium difficile* infection and hypomagnesaemia will be recorded at each study visit following randomisation

- progression free survival (with progression defined as time from date of randomisation to week of all-cause death, lung transplant, a 10% absolute reduction in FVC % predicted from baseline measured by domiciliary spirometry)
- hospital-free survival defined as death (all causes) or first non-elective (all cause) hospital admission
- Respiratory related hospital free survival

6.5.3 Study within a Trial (SWAT): The influence of patient support group delivered research awareness strategies on research recruitment and retention.

The TIPAL Study Within A Trial (SWAT) is designed to evaluate the potential of patient support groups to improve recruitment and retention rates in clinical trials. Recruitment rates can be poor and many patients, who are keen to be involved in clinical trials, are denied the opportunity to participate because they are not informed about the research. Patients are keen to ensure that clinical trials are delivered quickly so that clinical research questions can be answered and are generally supportive of research. Patient support groups often have a remit of promoting and supporting research. Action for Pulmonary Fibrosis (APF) is the UK national ILD charity with a remit to support patient support groups, give patients a voice, raise awareness of ILD and support research. There are nearly 50 ILD patient support groups in the UK and all specialist centres potentially involved with TIPAL have an affiliated support group. ILD patient support groups meet every 2-4 months, with interim mailing of newsletters, and groups are attended by between 20 and 60 patients or relatives.

We will perform a cluster-randomised pilot trial of patient-facilitated research awareness involving at approximately 20 sites within the UK. Recruitment for the SWAT will be stratified for impact rating (a score given by APF to reflect attendance, engagement and function of the group). The intervention will last for 12 months. It will include patient support group recruitment and retention initiatives, described in a training manual, with support from APF. After an assessment of the methods and impact, a revised intervention will be rolled out to the control sites to maximise recruitment into the study.

We will assess the impact by capturing the following at 12 and 24 months from the end of the development phase:

1) The number of self-reported self-referrals or enquires to participate in research studies as obtained from an exit questionnaires provided to all patients from all support groups.
2) The number of participants recruited via patient support group as obtained from site recruitment logs.
3) The number of hits on the study websites. We will capture this at individual site level by using the bitly.com redirecting website.
4) The completeness of the primary endpoint data.
5) The general knowledge and enthusiasm about research as well as the degree of empowerment and motives for participating in research, plus adverse or unintended consequences, from an exit questionnaire provided to all participants from all support groups.

We will not undertake a formal qualitative analysis however, descriptions of the initiatives used by different sites by questionnaire from site research champion will be discussed by a review group comprising members of APF and other members of the TIPAL team. This will permit further refinement

of the intervention before rolling out to the control group. The resources and costs of using the revised intervention will be estimated.

Further details of the TIPAL SWAT are provided in a separate protocol. The SWAT will be registered independently of the main trial in accordance with local and regulatory requirements.

6.6 Participant Timeline

Figure 2. Schedule of Assessments

	Screening[1]	Baseline[1]	Randomisation	3 Months[2, 3] (+/- 2 weeks)	6 Months[3, 4] (+/- 4 weeks)	9 Months[3, 4] (+/-4 weeks)	12 Months[3,4] (+/-4 weeks)
Informed Consent	X						
Eligibility	X						
Demographics, medical history and patient characteristics collected		X					
Randomisation			X				
IMP dispensed			X		X		
IMP adherence					X		X
Weekly domiciliary spirometry	←		Undertaken **weekly throughout** trial		→		
Lung function (including spirometry & gas transfer assessments) <u>where possible</u> see section 6.10.1		X		X	X		X

	Screening[1]	Baseline[1]	Randomisation	3 Months[2, 3] (+/- 2 weeks)	6 Months[3, 4] (+/- 4 weeks)	9 Months [3,4] (+/-4 weeks)	12 Months[3, 4] (+/-4 weeks)
Cough count sub-study		X		X			
Leicester Cough Questionnaire, MRC Dyspnoea Scale, King's Brief ILD Questionnaire, EQ-5D-5L & Cough score questionnaire		X		X	X	X	X
Study specific questionnaire		X					X
STOP-Bang Questionnaire							X
Short Pittsburgh Sleep Quality Index and DeMeester Score		X		X			X
Adverse events				X	X	X	X
Safety bloods (FBC, U&Es, LFT, Calcium and Magnesium)[5]		X		X	X	X	X

	Screening[1]	Baseline[1]	Randomisation	3 Months[2, 3] (+/- 2 weeks)	6 Months[3, 4] (+/- 4 weeks)	9 Months[3, 4] (+/-4 weeks)	12 Months[3,4] (+/-4 weeks)
Blood sample for genotype analysis[6]		X		X	X	X	X
Research bloods[7]		X					X

[1] Where participants are not attending in person consent, spirometry, cough count sub-study and collection of up to date trial data not available in the patient notes will take place remotely via phone/video call. Questionnaires will be completed and returned by freepost/courier/electronically. Safety bloods will be taken at GP surgery or site.
[2] Visit should take place within 2 weeks either side of the scheduled date.
[3] Where participants are not attending in person adverse events recorded during phone/video call with questionnaires completed and returned by freepost/courier/electronically and safety bloods taken at GP surgery or site. Cough count sub-study monitoring will be conducted remotely via phone/video call, or in person, at 3 months for sub-study participants.
[4] Visits should take place within 4 weeks either side of scheduled date.
[5] 10mls blood to be taken for safety analyses at all study timepoints.
[6] 10mls blood to be taken for genotype analysis **once** throughout the study **at any timepoint.**
[7] 20mls blood to be taken for research blood analyses at baseline and 12 months where possible.

NB where study assessments are completed within 28 days of randomisation for baseline or within the timeframes specified above, these observations can be recorded at the relevant time point to avoid patients having to repeat assessments unnecessarily provided they adhere to the requirements of this protocol.

Participants are permitted to repeat baseline FVC measurements upon receipt of the domiciliary spirometer to familiarise themselves on use of the equipment. Baseline FVC measurements should be attempted for a period up to a maximum of 14 days upon which, a decision as to whether to proceed to trial enrolment will be made by the local PI in collaboration with the CI and patient where appropriate if clinically consistent results have been challenging to obtain. Baseline and 12 month domiciliary spirometry measurements should be repeated daily for 5 days.

6.6.1 Participant Assessments

6.6.1.1 Visit settings

All study visits may occur at the recruiting site or remotely e.g. at the participant's home with safety bloods taken at the participant's GP surgery. Each visit will occur in the setting best suited to the participant and the recruiting site. The study is intended to be conducted remotely throughout if required, as such there is no minimum on-site visit requirement.

Where remote visits are conducted, research staff will conduct phone / video calls to counsel participants where necessary i.e. in completion of domiciliary spirometry assessments, fitting cough monitors, to collect updated/trial data etc.

In the event that participants attend the site for standard care appointments and complete full lung function tests including spirometry and gas transfer assessments, this data should be entered onto the BTS IPF registry. Domiciliary spirometry assessments must continue to be completed weekly as outlined in section 6.10.1.

Where safety bloods are to be taken at the participant's GP surgery, site staff will need to request the bloods are taken, ensure they are received and processed at the local laboratory and an authorised clinician will need to review the results at each timepoint.

6.6.1.2 Screening

The PI or delegate is responsible for identifying eligible patients to invite to participate in the study in accordance with the eligibility criteria defined in section 6.3.1. Eligible patients will be approached in clinic or identified via a local database/IPF patient list or clinical records and provided with the relevant study specific literature explaining the aims, methods and potential hazards and benefits of participation in the trial (see section 6.8.1) either in person or by mail. Patients will be given adequate time to consider their participation prior to the site seeking written informed consent electronically or paper-based following consultation in person or via phone/video call. Informed consent will be sought prior to completion of any assessments/procedures etc. required by the study outside the remit of usual care for patients in the same situation.

Consenting patients will receive a TIPAL study supplies kit containing a CE marked domiciliary spirometer with an adequate supply of mouthpieces for the trial participation period, a smart device (i.e. smartphone or tablet) with pre-installed software required for the study (and a pre-loaded data sim card if necessary) for use during the trial. Patients consenting to the sub-study will also receive a cough monitor, and may receive a wrist-based accelerometer, with instructions for return, contact details for IT support if needed and 'frequently asked questions' guidance.

Baseline FVC measurements should be attempted for a period up to a maximum of 14 days.

PPI use has been associated with an increase of 25-50% in osteoporosis(33). This should be considered, along with other risk factors for osteoporosis, by the recruiting clinician prior to enrolment in the trial who may wish to increase measures for reducing osteoporosis risk.

6.6.1.3 Baseline

Once written informed consent has been obtained, either in person, electronically or remotely via video/phone, the patient will be required to complete the following baseline assessments: domiciliary spirometry assessments, Leicester Cough Questionnaire, MRC Dyspnoea scale, K-BILD questionnaire,

EQ-5D-5L questionnaire, a study-specific questionnaire, cough score questionnaire, short Pittsburgh Sleep Quality Index, DeMeester score, safety bloods, genotype and research bloods where possible, and laboratory spirometry _+/- gas transfer were possible. Patient demographics, smoking status (including vaping), alcohol intake, body mass index (BMI), co-morbidities and relevant medical history and concomitant medication (including over-the-counter antacids) will be recorded in the eCRF. Where possible this data will be obtained from the BTS Registry, otherwise patient notes will be reviewed or patients asked directly for the relevant data.

Blood samples (full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs), calcium and magnesium) will be taken for safety purposes at the GP surgery or recruiting site prior to enrolment. Results of safety bloods taken at the GP surgery must be reviewed by an authorised clinician. Where participants are attending baseline visits at the recruiting centre, and provided it is feasible and the participant is willing to do so, a separate research blood sample will be taken. A further blood sample will also be taken and stored for genotyping for consenting participants (see section 6.6.2 for sample details); this will be taken once only at the recruiting site and may be taken at any timepoint following consent.

Domiciliary spirometry assessment guidance is provided in section 6.10.1. Participants will be trained by video/phone call(s) with trained staff on how to reliably complete domiciliary spirometry assessments throughout the study. Participants should complete spirometry assessments daily for 5 days at this timepoint.

Where the abovementioned assessments and/or data is captured as part of standard care within 28 days of randomisation within the requirements of this protocol, these observations may be recorded as the baseline values to avoid patients having to repeat procedures unnecessarily.

Participants eligible and consenting to the cough sub-study at applicable sites will also be required to undergo objective cough monitoring prior to starting trial treatment. Participants will be provided with a wearable cough recording device, a VitaloJAK monitor, to capture cough count over a 24 hour period. In addition, sub-study participants may also be invited to wear a wrist-based accelerometer during this 24h period to monitor activity levels and sleep concurrently. Activity and sleep monitoring is an optional additional component of the sub-study; participants are therefore able to participate in the cough monitoring aspect only. Sites/research staff will be trained in counselling participants on safe, accurate and reliable use of the devices and data extraction and processing following the monitoring period prior to activation to recruitment. Participants may be fitted with the cough monitor in person where visits to the recruiting site are completed or participants may be counselled to fit the monitors remotely via video/phone calls with trained staff. Cough, and activity, monitors will be returned to the recruiting site or trials unit by courier upon completion of the monitoring period.

Questionnaires will be completed on paper or electronically. During the consent process participants will be offered the option to complete questionnaires electronically. In this instance participants will complete all relevant questionnaires electronically via REDCap at each study time point. Participants opting not to receive the questionnaires electronically will complete paper copies of each questionnaire at each visit for return via courier or freepost.

6.6.1.4 Randomisation

Upon completion of and when results of all baseline assessments are known, site staff delegated the appropriate responsibility will be have the option to randomise the patient. Treatment allocation will be determined by a computer generated randomisation code via a web-based system facilitated by NCTU. A semi-blinded randomisation outcome will be circulated via email to the central research pharmacy only. The site PI and delegates will receive a blinded randomisation notification email.

An initial 6 month supply of IMP will be dispensed by the central research pharmacy following confirmation of treatment allocation and receipt of a completed trial prescription signed by the PI or delegated sub-investigator. The central research pharmacy are responsible for arranging shipment to the participant.

Participants will be instructed to commence **weekly** domiciliary spirometry measurements **from the date of receipt of their study drug.**

The participant's General Practitioner (GP) will be informed of the patient's randomisation into the study.

6.6.1.5 3 Months

The following assessments should be completed 3 months post-randomisation: full lung function (including spirometry and gas transfer assessments) where possible, domiciliary spirometry, Leicester cough questionnaire, MRC dyspnoea scale, K-BILD questionnaire, EQ-5D-5L questionnaire, cough score questionnaire, short Pittsburgh Sleep Quality Index, DeMeester score, adverse events and safety bloods (FBC, U&Es, LFTs, calcium and magnesium).

Site staff will contact participants by phone/video call to assess adverse events and any changes to concomitant medication and/or medical history where visit occurs remotely.

Safety bloods will be taken at the recruiting site where feasible or at the participants GP surgery for remote visits. Results of safety bloods taken at the GP surgery must be reviewed by an authorised clinician. Genotype blood samples may be collected for consenting participants only if visit occurs on site and a sample has not been obtained previously.

Participants will be retrained in completing domiciliary spirometry assessments if needed.

Where these assessments are completed as part of standard care and within the time frame permitted by and requirements of this protocol, the results may be recorded for those required at the 3 month study time point.

Participants completing paper-based questionnaires will be provided with a freepost envelope to return them to the trials unit otherwise they will be completed electronically via REDCap.

Cough sub-study participants will again be required to complete objective cough monitoring over a 24 hour period at applicable sites. Participants will be provided with a wearable VitaloJAK device to monitor cough frequency. In addition, participants may again be invited to wear a wrist-based accelerometer to measure concurrent activity levels and sleep during this 24h period. Where this visit occurs remotely, participants will again be counselled in fitting the device(s) and initiating recording.

A courier will again be arranged to collect the device(s) from the participant's home for return to the recruiting site or trials unit.

This visit may take place +/- 2 weeks of the scheduled date.

6.6.1.6 6 Months

The following assessments should be completed 6 months post-randomisation: full lung function (including spirometry and gas transfer assessments) where possible, domiciliary spirometry, Leicester cough questionnaire, MRC dyspnoea scale, K-BILD questionnaire, EQ-5D-5L questionnaire, cough score questionnaire, adverse events and safety bloods (FBC, U&Es, LFTs, calcium and magnesium).

IMP adherence will be measured by a pill count completed by site staff/participant during the visit. This may be conducted at site where visits take place in person or participants will be asked confirm the number of remaining capsules via phone/video call. If the participant has reduced their trial treatment dose due to adverse reaction(s) this should be documented in the eCRF and a new dosing card administered. Participant should return the superseded dosing card either in person or via freepost envelope.

Site staff will contact participants by phone/video call to assess adverse events and any changes to concomitant medication and/or medical history where visit occurs remotely.

Safety bloods will be taken at the recruiting site where feasible or at the participants GP surgery for remote visits. Results of safety bloods taken at the GP surgery must be reviewed by an authorised clinician. Genotype blood samples may be collected for consenting participants only if visit occurs on site and a sample has not been obtained previously.

Participants will be retrained in completing domiciliary spirometry assessments if needed.

Participants completing paper-based questionnaires will be provided with a freepost envelope to return them to the trials unit otherwise they will be completed electronically via REDcap.

Where these assessments are completed as part of standard care and within the time frame permitted by and requirements of this protocol, the results may be recorded for those required at the 6 month study time point.

Participants will be supplied with a final 6 month supply of IMP as prescribed by the PI or delegate, dispensed by the central research pharmacy. Site staff to ensure patient is administered dosing card with correct treatment schedule. The central research pharmacy are responsible for arranging shipment to the participant.

Where these assessments are completed as part of standard care and within the time frame permitted by and requirements of this protocol, the results may be recorded for those required at the 6 month study time point.

This visit may take place +/- 4 weeks of the scheduled date.

6.6.1.7 9 Months

The following assessments will be completed 9 months post-randomisation: Leicester cough questionnaire, MRC dyspnoea scale, K-BILD, EQ-5D-5L,cough score questionnaire, safety bloods (FBC, U&Es, LFTs, calcium and magnesium) and adverse events.

Participants will be provided with a free post envelope to return completed paper-based questionnaires to the trials unit otherwise they will be completed electronically via REDcap.

Site staff will contact the participant via phone/video call to record any adverse events experienced and any changes to concomitant medication and/or medical history where this visit occurs remotely.

Safety bloods will be taken at the recruiting site where feasible or at the participants GP surgery for remote visits. Results of safety bloods taken at the GP surgery must be reviewed by an authorised clinician. Genotype blood samples may be collected for consenting participants only if visit occurs on site and a sample has not been obtained previously.

Participants will be retrained in completing domiciliary spirometry assessments if needed. This visit may take place +/- 4 weeks of the scheduled date.

6.6.1.8 12 Months

The following assessments should be completed 12 months post-randomisation: full lung function (including spirometry and gas transfer assessments (where possible), domiciliary spirometry, Leicester cough questionnaire, MRC dyspnoea scale, K-BILD questionnaire, EQ-5D-5L questionnaire, cough score questionnaire, study specific questionnaire, DeMeester score, STOP-bang questionnaire, the short Pittsburgh Sleep Quality Index questionnaire, adverse events, safety bloods (FBC, U&Es, LFTs, calcium and magnesium) and research bloods where possible.

IMP adherence will be measured by a pill count completed by site staff/participants during the visit. If the participant has reduced dose due to adverse reaction(s) this should be documented in the eCRF. This may be conducted at site where visits take place in person or participants will be asked confirm the number of remaining capsules via phone/video call. Dosing card(s) should also be returned.

Safety bloods will be taken at the recruiting site where feasible or at the participants GP surgery for remote visits. Results of safety bloods taken at the GP surgery must be reviewed by an authorised clinician. Genotype blood samples may be collected for consenting participants only if visit occurs on site and a sample has not been obtained previously. Research bloods will be taken separately if possible during an in person visit at the recruiting site (see section 6.6.2 for sample details).

Participants should complete spirometry assessments daily for 5 days at this timepoint.

Site staff will contact participants by phone/video call to assess adverse events and any changes to concomitant medication and/or medical history where visit occurs remotely.

Participants completing paper-based questionnaires will be provided with a freepost envelope to return them to the trials unit otherwise they will be completed electronically via REDCap.

The TIPAL study supplies (domiciliary spirometer and smart device) should be returned in person to site or via courier to the trials unit upon study completion. Equipment returned in person to recruiting sites will be returned to the trials unit periodically.

Where these assessments are completed as part of standard care and within the time frame permitted by and requirements of this protocol, the results may be recorded for those required at the 12 month study time point.

This visit may take place +/- 4 weeks of the scheduled date.

6.6.2 Human Tissue Samples

10mLs of whole blood will be taken for safety at baseline, 3, 6, 9 and 12 months post-randomisation. These may be taken and processed at the recruiting site, or taken at the participant's GP surgery and shipped for processing at the recruiting site in accordance with local standard procedures.

10mLs of whole blood for genotype analysis will be taken at the recruiting site from consenting participants only **once at any timepoint** during their participation. If appropriately consenting participants do not attend any study visits in person at the recruiting site, it will not be possible to obtain a sample for genotype analysis.

20mLs of whole blood for future research purposes will be taken at baseline and 12 months post-randomisation at the recruiting site where possible. As study visits may be conducted remotely, it may not be possible to obtain samples from all participants at any or both timepoints. Zero, one or both research blood samples will be obtained from participants willing to provide samples for analysis in future research projects where possible.

Relevant samples will stored at -80°C at recruiting sites, and transported to the Norwich Research Park Biorepository for genotyping or future analysis of any potential biomarker including but not limited to interstitial lung disease, infection or reflux, pending additional ethical approval, at a later date.

Sample handling training will be provided to all sites prior to activation detailing sample collection, handling and storage procedures. Sites are responsible for ensuring samples collected at GP surgeries are requested, taken, shipped, processed, reviewed and reimbursed in accordance with standard NHS procedures. Detailed written instructions and appropriate tissue transfer agreements will be put in place prior to the transfer of relevant material.

6.6.3 Early Stopping of Follow-up

Sites must inform NCTU of all forms of early trial discontinuation via the eCRF. In instances where a participant has decided to withdraw consent, it is essential for the site to establish which aspects of the trial the participant is withdrawing consent from.

- If a participant chooses to discontinue their trial treatment, 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 encouraged and facilitated not to leave the whole trial, even though they no longer take the trial treatment.
- If a participant who has discontinued trial treatment no longer wishes to attend any remaining follow-up visits, relevant follow up data will continue to be collected from the registry during the trial providing the participant is willing for this to continue.
- If, however, the participant exercises the view that they no longer wish to provide data either through study visits or remotely via the registry, this view must be respected and the participant withdrawn entirely from the trial. Data already collected will be kept and included

in analyses according to the intention-to-treat principle for all participants who stop follow up early. Any samples provided by the participants, which have yet to be analysed will be destroyed and the registry will be updated so that no further data is provided to NCTU.

Where patients are unable or unwilling to continue to undertake study measurements/activities, the decision as to whether the participant should continue with trial treatment and/or follow-up assessments will be at the discretion of the local PI and/or CI.

Participants who stop trial follow-up early will not be replaced.

6.6.4 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-up at another participating trial centre. Written consent should be taken at the new centre, either electronically or paper-based following consultation either in person or via video/phone call, 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.

6.6.5 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 of whether they have withdrawn from the intervention or study assessments. Patients will be asked to provide consent so that all follow-up information on overall or hospital free survival can be obtained from the BTS registry if required.

6.6.6 Trial Closure

The end of the trial is defined as 4 months following the last follow-up visit of the last patient randomised, to allow for data entry and data cleaning activities to be completed.

6.7 Sample Size

A sample size of 270 individuals, 135 per group, will provide 90% power to detect a minimal important difference (MID) of 4% reduction in % FVC versus placebo assuming a standard deviation of 9% (from the TIPAC trial) and a loss to follow-up rate of 20% (from the TIPAC and EME-TIPAC trials) and a significance level of 5%. However, we will randomise 298 patients (149 per group) in order to account for 10% of patients being asymptomatic.

A sample size of 160 patients (80 per group) will provide 90% power to detect a ratio of geometric means of 0.6 of cough frequency, which is smaller than the published MID (47), assuming a coefficient of variation of 1 (from the PPIPF trial) and a loss to follow-up rate of 30%.

The sample size was based on references which used lab-based spirometry devices, due to COVID-19 the measurement that will be used is the home-based spirometry. The trial team felt it was simpler to leave the sample size as it was originally as there is a lack of data available on the variability of the outcome in the devices used and no reason to think that the MID would be different due to the different devices. The DMC will monitor the assumptions of the sample size calculation in accordance with the Terms of Reference.

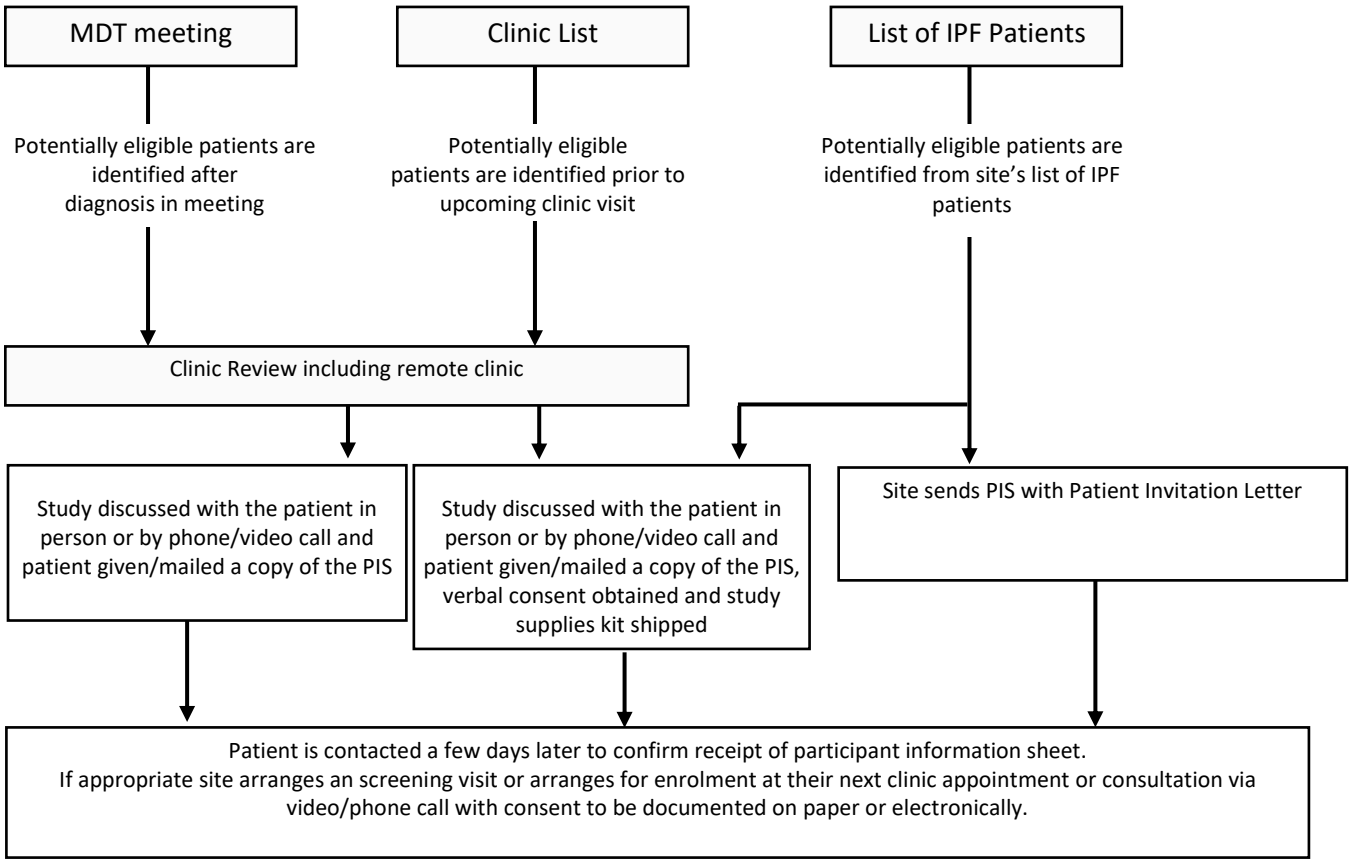
6.8 Recruitment and Retention

6.8.1 Recruitment

Patients will be identified mainly by review of ILD 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, summarised in figure 3, 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 paper which provides an overview of the study and a participant information sheet. The clinic staff will arrange a subsequent screening visit.
- The clinic team may also mail (by post or e-mail) an invitation letter with or without a participant information sheet along with a contact email address/phone number to respond to, 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 (by post or e-mail) an invitation letter on hospital headed paper which provides an overview of the study, and a participant 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.
- Patients may be approached as outlined above, seeking initial verbal consent to participate in the study and for their contact details to be shared with the NCTU trial team to be documented in the patient notes. Following verbal consent, NCTU staff may arrange/oversee shipment of the TIPAL study supplies kit including a smart device to allow e-consent to be completed and the remaining assessments to be completed from baseline onwards as long as the participant remains willing.

Figure 3: TIPAL Recruitment Strategies



Potential patients may be contacted by phone between 3 and 7 days after the mailing of the letter/sending the email to ensure that they have received it. Enrolment will then be scheduled either via a face-to-face visit or by consultation via phone/video call for those willing to consent to participate. Potential participants and site staff will confirm whether consent will be recorded electronically or on paper, with the decision documented in the patient's medical notes, to facilitate preparations for the enrolment visit.

Remote consent

For those being enrolled remotely and completing paper consent forms, a localised consent form with a freepost or stamped address envelope, will be mailed to the potential participant for their completion following the study consultation. The person taking consent will countersign the form upon receipt at the recruiting site.

Where electronic consent is being sought, participants will verbally consent to the sharing of their email address and/or contact details in order to receive the link to the electronic consent form to facilitate the process. This will be documented by site staff in the patient's medical notes. Both parties will complete the electronic consent form following the phone/video call consultation by providing a wet-ink signature equivalent on the designated field via REDcap (51).

Details of the consultation, including but not limited to the time/date of the phone/video call, confirmation of identification checks and the name of the staff member leading the call and thus

taking consent will be recorded in the patient's medical notes. Copies of the completed forms will be mailed (by post or email) to participants.

Consent will be obtained prior to any study related procedure. Following consent, screening bloods will be taken and other eligibility criteria will be assessed. Patients meeting all entry criteria (after review of screening bloods) and willing to consent to participate or having already provided consent, will be sent a TIPAL study supplies kit including the spirometer and smart device. Participants may be randomised without a subsequent visit. Medication will be dispensed by the central study pharmacy and couriered (or sent via another signed for delivery service) directly to the participant and will require signature on receipt. Participants will be advised to store their medication below 25°C but there may not be any temperature monitoring after IMP has been dispensed.

6.8.2 Retention

This study has been designed to be able to be conducted completely remotely reducing participant burden significantly by removing travel time and associated cost(s), allowing almost complete flexibility around completion of study assessments and removal of any risks associated with breaking COVID-19 social distancing guidelines. A remote study design also means trial participation can continue in the event of local lockdowns for any reason. Maintaining additional contact outside of standard clinic appointments may also encourage retention.

The provision of a smart device, with a pre-loaded sim card if required and regular support where needed, affords all participants equal opportunity to participate despite any personal technological inequalities.

Postage for participants opting to complete paper-based questionnaires and costs associated with couriering TIPAL study supplies kits including equipment required for the sub-study and IMP to, and from, where applicable, participants are not payable by participants at any point. Couriers will be scheduled following consultation with the participant where possible to ensure collection/delivery is convenient to the participant.

Participants will also be offered the option to subscribe to an email based participant newsletter during the study's recruitment period in order to help keep participants engaged and informed of study progress during and beyond their participation.

The SWAT is also intended to improve participant retention at intervention sites.

Participants will be given/posted a card with the contact details of the local PI that will request details of hospital admissions to be reported at consent/baseline. Patients will be asked to provide informed consent for their contact details to be stored in a trial contacts database at UEA. Participants 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) baseline licensed medication for IPF (yes/no), iii) reflux symptoms (presence/absence) and iv)

persistent cough (presence/absence). 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 (TIPAL Allocation Schedule) stored in a shared file accessible to only the study statistician(s) and data management team as appropriate.

6.9.1.2 Allocation concealment mechanism

Allocation will be computer generated by a web-based system ensuring concealment prior to randomisation. Following consent and confirmation of eligibility the PI or delegate will enter data confirming eligibility into the eCRF generating a participant identification number. Blinded notification of randomisation will be sent to the PI and/or delegates, CI and NCTU trial team. A semi-blinded notification of randomisation will be sent to the central pharmacy.

6.9.1.3 Allocation Implementation

The PI or delegated sub-investigator is responsible for ensuring only eligible patients are randomised and prescribed study medication. 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.

6.9.2 Blinding

This is a double blind study. The placebo and active treatments will appear identical and will be dispensed in identical containers. All trial participants, care providers and outcome assessors 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 CI 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 the CI who will authorise unblinding by the Data Management Team. All instances of unblinding should be recorded and reported to NCTU by the local PI, or delegate, including the identity of all recipients of the unblinding information.

6.9.3 Non-emergency Unblinding

For circumstances where non-emergency unblinding is required e.g. GP/clinician or participant request, following confirmation from the CI, treatment allocation will be revealed by the eCRF, using log-ins and forms separate to those required to unblind in emergency situations. The blind will be

maintained for as many of the local study and NCTU trial team members as possible. A record of non-emergency unblinding and those individuals unblinded to trial treatment will be recorded and filed.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

An on-line patient screening log will contain the details of the patient initials, date of contact and the route of identification for all potential participants who have received a patient information sheet (PIS). Following confirmation of consent, each participant will be given a unique trial Participant IDentification Number (PID). Data will be collected at the time-points indicated in the Schedule of Assessments (see section 6.6).

Data collection will vary according to the data variable in question.

Laboratory spirometry will be captured according to European Respiratory Society (ERS)/American Thoracic Society (ATS) criteria(50) by an Association for Respiratory Technology & Physiology (ARTP) registered pulmonary function technologist (see relevant working instruction available from NCTU trial team) where possible.

Once erroneous blows have been rejected as required, the FVC for the highest three blows will be recorded.

Gas transfer measurements will be performed to ERS/ATS standards(48) by an ARTP registered pulmonary function technologist. Domiciliary spirometers are provided to participants following consent to obtain weekly spirometry data from receipt of the study drug to 12 months post-randomisation. Participants will be asked to perform at least three forced expiratory volume manoeuvres. Measurements will be made on 5 consecutive days at baseline and at twelve months and once weekly for the remainder of the study. The domiciliary spirometer will transfer data for each blow via Bluetooth to the accompanying app pre-installed on the smart device provided. The assessments will be graded according to ERS/ATS criteria (50) within the app. The raw data including flow-volume loops and volume-time curves will be automatically synced from the app on the participant's smart device to a validated clinical trials data platform or entered into the eCRF.

The following variables will be recorded during domiciliary spirometry assessments and recorded onto the accompany clinical trials data platform or eCRF and/or should be observed during lung function (including spirometry and gas transfer assessments) and recorded onto the BTS registry/eCRF as required where assessments are possible:

- FEV1
- FVC
- DLCO
- KCO
- The FEV1/FVC ratio will be calculated from the data provided.

Further guidance for the conduct of domiciliary spirometry assessments is provided in the corresponding TIPAL working instruction available from the NCTU trial team. Participants will also be provided with ethically approved literature to assist them in the completion of their spirometry assessments in addition to the guidance given by the app during the measurements.

Where participants complete lung function assessment including spirometry and gas transfer assessments in the laboratory, FEV1, FVC, DLCO, KCO and subsequently calculated FEV1/FVC ratio will be recorded in the BTS IPF registry.

Participants will be asked to complete online questionnaires but there will be a provision of completing the questionnaires on paper if required. Paper questionnaires will be sent to NCTU (by post or email using high resolution scanning), where they will be read using optical character recognition software and the resulting data imported into the study database. Online responses will be stored directly in the eCRF.

Relevant data will be exported at regular intervals and imported into the study database. The datasets will be matched on the TIPAL PID, which will be stored in the BTS Registry and domiciliary spirometer clinical data platform if applicable. The BTS Registry IDs will be stored in the TIPAL study database as a means of double-checking the correct records have been imported. Patient consent will be sought prior to data sharing.

Data required only for study purposes will be entered by direct online entry into the eCRF by delegated members of research site staff.

Positive tests for covid-19 during trial participation will be recorded on the eCRF following a review of patient medical notes/discussion with participants by site staff. Covid-19 infection will be confirmed at baseline and at each study visit thereafter as part of the adverse event review.

Further information on data collection and management processes are provided in the TIPAL Data Management Plan.

Data may be entered onto paper Case Report Forms (CRFs) prior to entry onto the database. Staff will receive training on data collection and use of the online system (see Section 6.10.2).

Data collection, data entry and queries raised by a member of the TIPAL trial team will be conducted in line with NCTU and trial specific Data Management Standard Operating Procedure.

Identification logs and enrolment logs will be kept at the trial site in a locked cabinet within a secured room.

Participant identifiable data will be stored on a Participants Database for the purpose of couriering IMP and TIPAL study supplies kits, contacting participants to collect trial data, arrange couriers etc., sending questionnaires and reminders and for sending newsletters during the trial. All participant identifiable data will be stored securely, with access only granted to those members of the study team who require it.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act 2018 and GDPR 2018 and any subsequent revisions.

6.10.2 Data Management

Data will be entered under the participants PID number onto the central database stored on the servers based at NCTU. Access to the database will be via unique, individually assigned (i.e. not generic) usernames and passwords, and only accessible to members of the TIPAL trial team at NCTU,

TIPAL study teams at sites and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected physically and environmentally in accordance with University of East Anglia's General Information Security Policy 3 (GISP3: Physical and environmental security).

Each participant will have a profile on the app which accompanies the domiciliary spirometer following consent. The app profile will contain clinically relevant data necessary to grade spirometry assessments and may contain some personal information to allow identification of the participant at the recruiting site and/or trials unit.

Cough count sub-study data will be held within a trial specific database developed and maintained by the cough monitor manufacturers. Participants will be identified by their PID. Access will be restricted to relevant members of the NCTU trial team, cough analysts, and authorised members of site staff at recruiting sites via a unique username and password. Site staff will have access to participant data recruited by their site only whereas the NCTU trial team, cough monitor manufacturer project team and cough analysts will have oversight of data for all trial participants.

The eCRF and associated code will be developed by NCTU Data Management, in conjunction with the TIPAL trial team. The eCRF software will provide 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.

After completion of the trial the eCRF will be retained for at least 5 years on the servers of NCTU for on-going analysis of secondary outcomes. Cough count sub-study data will be retained by Vitalograph for at least 25 years.

The identification and enrolment logs, linking participant identifiable data to the pseudoanonymised PID, will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected forms on hospital computers. After completion of the trial the identification and enrolment logs will be stored securely by the sites for 5 years unless otherwise advised by NCTU.

6.10.3 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 capsule counts of unused returned drug supplies at each relevant study visit.

Where patients are unable or unwilling to continue to undertake study measurements/activities, the decision as to whether the participant should continue with trial treatment and/or follow-up assessments will be at the discretion of the local PI and/or CI.

6.10.4 Statistical Methods

6.10.4.1 Outcomes

Primary outcome

The primary outcome, absolute change in %FVC at 12 months post-randomisation, will be analysed using a general linear model adjusting for the minimisation factors used in the allocation algorithm. The average of the best value undertaken each day over a 5 day period will be calculated. An adjusted analysis will also be undertaken adjusting for the baseline %FVC. Additional adjusted analysis may be undertaken for factors associated with the outcome. In addition, a linear mixed model will be used to combine all the post-randomisation %FVC results into a single model which will adjust for the same factors and include a patient identifier as a random effect. An interaction between group and time will also be included to assess if the effect of the intervention is constant over time or varies as time progresses. A sensitivity analysis will be undertaken excluding asymptomatic individuals.

Secondary outcomes

The decline and rate of decline in %FVC during the 12 months: This will be based on a longitudinal model with a factor for the intervention or control to represent the average change over the course of the trial, and a time-trend to represent the decline in %FVC during the 12 months of the control group, and a time-trend x intervention interaction to represent the additional decline in %FVC during the 12 months. If there is evidence of a non-linear time trend, then to ease interpretation, the data will be averaged to the average %FVC each month and time will be treated as categorical. Different temporal correlation structures will be investigated.

Cough frequency: This will be based on a log-transformed cough count at 3 months, the model used will be a general linear model adjusting for the minimisation factors used in the allocation algorithm. An adjusted analysis will also be undertaken adjusting for baseline cough count. The effect size will be estimated as the geometric mean.

Cough score: This will be based on a general linear model with cough score at 12 months as the outcome, adjusting for the minimisation factors used in the allocation algorithm. An adjusted analysis will also be undertaken adjusting for baseline cough score. The effect size will be estimated as the mean difference. In addition, a linear mixed model will be used to combine all the post-randomisation cough score results into a single model which will adjust for the same factors and include a patient identifier as a random effect. An interaction between group and time will also be included to assess if the effect of the intervention is constant over time or varies as time progresses.

Cough related Quality of Life (QoL): This will be based on a general linear model with cough related QoL at 12 months as the outcome, adjusting for the minimisation factors used in the allocation algorithm. An adjusted analysis will also be undertaken adjusting for baseline cough related QoL. The effect size will be estimated as the mean difference. In addition, a linear mixed model will be used to combine all the post-randomisation cough related QoL results into a single model which will adjust for the same factors and include a patient identifier as a random effect. An interaction between group and time will also be included to assess if the effect of the intervention is constant over time or varies as time progresses.

MRC dyspnoea scale: This will be based on a Mann-Whitney U test comparing the MRC dyspnoea scale at 12 months between groups. It will not be possible to adjust for the minimisation factors used in the allocation algorithm or to report an effect size, however the median in each group will be reported. As the same analysis will be conducted at 3,6 and 9 months a Bonferroni adjustment will be made to the p-values.

King's Brief Interstitial Lung Disease (K-BILD): This will be based on a general linear model with K-BILD as the outcome, adjusting for the minimisation factors used in the allocation algorithm. An adjusted analysis will also be undertaken adjusting for baseline K-BILD. The effect size will be estimated as the mean difference. In addition, a linear mixed model will be used to combine all the post-randomisation K-BILD results into a single model which will adjust for the same factors and include a patient identifier as a random effect. An interaction between group and time will also be included to assess if the effect of the intervention is constant over time or varies as time progresses.

EQ-5D-5L: This will be based on a general linear model with EQ-5D-5L as the outcome, adjusting for the minimisation factors used in the allocation algorithm. An adjusted analysis will also be undertaken adjusting for baseline EQ-5D-5L. The effect size will be estimated as the mean difference. In addition, a linear mixed model will be used to combine all the post-randomisation EQ-5D-5L results into a single model which will adjust for the same factors and include a patient identifier as a random effect. An interaction between group and time will also be included to assess if the effect of the intervention is constant over time or varies as time progresses.

DLCO: This will be based on a general linear model with DLCO as the outcome, adjusting for the minimisation factors used in the allocation algorithm. An adjusted analysis will also be undertaken adjusting for baseline DLCO. The effect size will be estimated as the mean difference. In addition, a linear mixed model will be used to combine all the post-randomisation DLCO results into a single model which will adjust for the same factors and include a patient identifier as a random effect. An interaction between group and time will also be included to assess if the effect of the intervention is constant over time or varies as time progresses.

Study-specific questionnaire: The analysis will be descriptive summarising the change in responses to each question from baseline. The acceptability of the treatment will be based on the response to questions five, six and seven.

Sleep apnoea: The STOP-Bang will be analysed by a low, intermediate or high risk using an oridinal logistic regression model adjusting for minimisation factors used in the allocation algorithm.

Sleep quality: The Pittsburgh score will be analysed using a general linear model, adjusting for minimisation factors used in the allocation algorithm. An adjusted analysis will also be undertaken adjusting for the baseline score.

Reflux characteristics: The DeMeester score will be analysed using a Mann-Whitney U test at each time-point.

Progression free survival: This will be assessed using the weekly home-based spirometry measures and hospital data. The effect size will be estimated as the hazard ratio. Cox proportional hazards will be used adjusting for the minimisation factors used in the allocation algorithm. Disease progression will be defined as date from randomisation until the week of all-cause mortality, lung transplant or a 10% absolute reduction in % FVC from baseline measured by domiciliary spirometry.

Unplanned hospital-free survival: This will be assessed at 3, 6, 9 and 12 months and will be presented as a number and percentage. The effect size will be estimated as the odds ratio. Logistic regression will be used adjusting for the minimisation factors used in the allocation algorithm.

Respiratory-related hospitalisation: This will be assessed at 3, 6, 9 and 12 months and will be presented as a number and percentage. The effect size will be estimated as the odds ratio. Logistic regression will be used adjusting for the minimisation factors used in the allocation algorithm.

The assumptions of all the models will be checked using residual analysis and, if appropriate, alternative methods will be used.

If there is sufficient non-compliance then a compliance-adjusted causal effect (CACE) analysis will be undertaken using the models above. In addition, if there is sufficient reduction in dose amongst participants, a dose-response relationship will be estimated using instrumental variable regression.

6.10.4.2 Statistical Analysis Plan (SAP)

A full SAP will be produced prior to the analysis of any data. Both the TSC and DMC will be given the opportunity to comment on the SAP prior to it being signed-off by the CI and lead statistician.

6.10.4.3 Additional Analyses

Study within a Trial (SWAT): The influence of patient support group delivered research awareness strategies on research recruitment and retention.

A descriptive analysis will be undertaken to compare the number of self-reported self-referrals or enquiries to participate in research studies from participants, the number of patients recruited via patient support groups and the number of hits on the study websites. We will also compare the completeness of the primary endpoint data at each site and the results from a questionnaire to assess general knowledge and enthusiasm about research as well as the degree of empowerment and motives for participating in research, plus adverse or unintended consequences.

The number of recruited participants per site: The analysis will be based on a random effects Poisson regression model with site included as a random effect and an offset of the size of the site.

Primary outcome completeness: The analysis will be based on a random effect logistic regression model with site included as a random effect.

6.10.4.4 Analysis Population

The analyses population are defined as:

a) intention-to-treat (ITT): all randomised individuals regardless of adherence
b) If compliance is less than 85% then a compliance adjusted causal effect (CACE) analysis will also be carried out defining compliance as taking at least 80% of study medication based on pill counts
c) safety population: all patients randomised who received at least one dose of the trial treatment

6.10.4.5 Missing Data

The pattern of missing data will be assessed and if appropriate, multiple imputation will be used to account for missing data under the assumption that the data are missing at random. If the data are not considered missing at random then a sensitivity analysis of the results will be undertaken by considering appropriate scenarios, such as the worst-case scenario or pattern-mixture models.

6.10.5 Economic evaluation

Formal economic evaluation will not be completed as part of this trial. However, use of health services recorded throughout the trial will focus on use of secondary care services as they are significant events for both patients and the NHS. These data will be reported as summaries and analysed using the methods described above.

6.10.6 Analysis of Tissue Samples

There is not any planned analysis of tissue samples other than safety analysis. Blood, serum and plasma will be stored for analysis in future studies following ethical approval.

A laboratory analysis plan for genotype samples will be agreed and approved by the CI and TMG prior to analysis. In addition, a laboratory manual for sample handling will be developed and agreed by the CI and circulated to sites prior to activation to recruitment.

6.11 Safety reporting

6.11.1 Safety reporting

Adverse events will be collected at each visit and analysed according to the SAP. Adverse events by treatment group will be reviewed regularly by the DMC as described in their Terms of Reference (ToR).

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

Table 2: 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/trial treatment.
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 SPC for an authorised product or treatment.
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***

* 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 for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE.

*** 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
- 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

AEs will be coded according to the current version of the Common Terminology Criteria for Adverse Events (CTCAE) dictionary.

6.11.2 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 on the adverse events form of the eCRF within 7 days of report/becoming aware.

All SARs and SAEs should be should be notified to NCTU immediately after the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

6.11.2.1 Seriousness assessment

When an AE or AR occurs, the investigator or delegated sub-investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 2. If the event is classified as 'serious' an SAE form must be completed and NCTU notified immediately. Investigators will also assess causality of the event(s) according to Table 3.

6.11.2.2 Severity or grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded according to CTCAE grading criteria and be assigned a grade 1-5.

6.11.2.3 Causality

The investigator must assess the causality of all serious events in relation to the trial treatment using the definitions in Table 3.

Table 3: Adverse Event 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 section 6.4.1.4 of this protocol.

6.11.2.4 Expectedness

If there is at least a possible involvement of the trial IMP (including any comparators), the investigator and NCTU must assess the expectedness of the event. An unexpected adverse reaction is one that is not reported in the approved SPC, or one that is more frequently reported or more severe than previously reported. See section 4.8 of the SPC for a list of expected reactions associated with the IMP being used in this trial. If a SAR is assessed as being unexpected, it becomes a suspected, unexpected, serious adverse reaction (SUSAR) and MHRA and REC reporting guidelines apply (see Notifications sections of the protocol section 6.11.3).

6.11.3 Notifications

6.11.3.1 Notifications by the Investigator to NCTU

NCTU must be notified of all SAEs immediately and no later than 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 SAE form must be completed by the investigator or sub-investigator (a clinician named on the delegation of responsibilities list who is responsible for the participant's care) with attention paid to the grading, causality and expectedness of the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. 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 will 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

Participants 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 redacted and replaced with trial identifiers on any test results.

6.11.3.2 NCTU responsibilities

Medically qualified staff at NCTU and/or the CI (or a medically qualified delegate) will review all SAE reports received and the NCTU trial team will notify the Sponsor as appropriate. 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 causality attributed to lansoprazole by the local investigator cannot be downgraded by other parties.

NCTU is responsible for the reporting of SUSARs 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 REC as appropriate. Fatal and life threatening SUSARs must be reported to the competent authorities within 7 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.

The trial manager or delegate at NCTU will submit Development Safety Update Reports (DSURs) to competent authorities.

6.12 Data Monitoring

6.12.1 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 TIPAL DMC ToR.

6.12.2 Interim Analyses

There are no interim analyses planned.

6.12.3 Quality Assurance and Control

6.12.3.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the TIPAL 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 participants; 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.

6.12.3.2 Central Monitoring at NCTU

NCTU staff will review the eCRF 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 TIPAL trial Data Management Plan. The quality of the domiciliary spirometry data will be monitored regularly during the study and at least at every 3 monthly visit. Participants will be retrained as required.

Patients are consented to enable NCTU to hold a copy of the completed consent form to allow central data monitoring checks to be completed.

6.12.3.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the TIPAL Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority, NCTU must be notified as soon as possible.

6.12.3.3.1 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.

6.12.3.4 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 participants, 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 TIPAL QMMP.

6.12.3.4.1 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.

6.12.3.4.2 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.

6.12.3.4.3 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. 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.

6.12.3.4.4 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to unblinded accumulating comparative data. The IDMC is responsible for safeguarding the interests of trial participants, 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 IDMC terms of reference. The IDMC will consider data in accordance with the SAP and will advise the TSC through its Chair.

6.12.3.4.5 Trial Sponsor

The role of the sponsor, Norfolk and Norwich University Hospitals NHS Foundation Trust, is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. The Sponsor is responsible for ensuring that the study meets the relevant standards, and makes sure that arrangements are put and kept in place for management, monitoring and reporting. A proportion of the Sponsor's activities have been delegated to the CI, UEA and NCTU as outlined on the form for delegated activities agreed and signed by all parties before the start of the trial.

7 Ethics and Dissemination

7.1 Research Ethics and Health Research Authority 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 and to HRA for approval. Any subsequent amendments to these documents will be submitted for further 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 protocol will be submitted to the MHRA.

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.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the MHRA in accordance with relevant requirements and practices.

7.3 Other Approvals

Documentation will need to be submitted to the R&D Department at each NHS Site in order to gain confirmation of capacity and capability prior to the study being initiated at that site. Confirmation from the site will take the form of a site agreement signed by the Sponsor, NCTU and the relevant site as required.

A copy of the local R&D approval and of the Participant Information Sheet (PIS) and consent form on local hospital headed paper must be forwarded to the co-ordinating centre before participants 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 Amendments

Amendments to the Protocol and other documents (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be agreed by the TMG. Such amendments will be forwarded to the Sponsor for confirmation as to whether it is either substantial or non-substantial and will then be submitted to the MHRA, HRA or Ethics Committee for categorisation and approval as required. Once the amendment has been categorised it will be sent to relevant sites for consideration in accordance with standard MHRA and/or HRA processes and timescales. Amendments must not be implemented until all approvals are received and sites have either confirmed acceptance or, no objection has been received within the defined timescale(s). Notification will be sent by NCTU to trial personnel to confirm when an amendment can be implemented.

A summary of protocol amendments will be maintained within the protocol.

7.5 Consent or Assent

Patients will be provided with a PIS and given time to read it fully. Following a discussion with a medical qualified investigator or suitably trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained either electronically or paper-based following consultation in person or via phone/video call. During the consent process it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their 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 participant 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 and PIS are available from the NCTU trial team.

7.6 Confidentiality

Any paper copies of personal trial data will be kept at the participating site in a secure location with restricted access.

Confidentiality of patient's personal data is ensured by not collecting patient names on CRFs and limiting access to personal information held on the database at NCTU. At trial enrolment the patient will be issued a participant identification number and this will be the primary identifier for the patient, with secondary identifiers of month and year of birth and initials.

The patient's consent form will carry their name and signature. These will be kept at the trial site, with a copy sent to NCTU for monitoring purposes. This copy will be destroyed/deleted once checks are complete. Consent forms will not be kept with any additional patient data.

Identifiable data will be shared with the NCTU trial team only following written informed consent or verbal consent from the patient to participate in the study. Personal data will be accessed to allow shipment arrangements for study supplies and IMP to be facilitated and to contact participants for (re)training in trial related procedures where necessary. Only authorised NCTU trial team members will have access to this data for the abovementioned purposes only and will ensure it is handled confidentially and in accordance with data protection regulations. Relevant identifiable data will be shared with central pharmacy and spirometer manufacturer staff and couriers only for shipping and administrative purposes only. In addition, some personal data will be stored within the app and data platform used to collate domiciliary spirometry data following consent of participants only, this will be held in accordance with data protection regulations and will not be shared with any third parties.

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

TIPAL is fully funded by National Institute for Health Research (NIHR) HTA grant reference number: NIHR127479. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

It is not expected that any further external funding will be sought

7.10 Archiving

The investigators agree to archive and/or arrange for secure storage of TIPAL trial materials and records for a minimum of 5 years after the close of the trial unless otherwise advised by NCTU. The Sponsor's trial master file will be archived in accordance with regulatory requirements and local policy.

7.11 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG and TSC. Considerations for approving access are documented in the TMG/TSC Terms of Reference.

7.12 Ancillary and Post-trial Care

There are no plans to offer trial treatment to individuals participating in this study after its conclusion. Lansoprazole is available on prescription should their usual care team wish to prescribe it.

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.

7.13.3 Reproducible Research

The trial will be registered on the International Standard Randomised Clinical Trials Number (ISRCTN) website granting public access to the trial outcomes. In addition the clinical study protocol will be submitted for publication. Every effort will be made to grant access to the participant level dataset subject to TSC approval.

7.14 Patient and Public Involvement

Patient and public involvement representatives will assist the TIPAL trial team in the design, management and undertaking of the study, and in the dissemination of trial results. Representatives will be consulted during the development of trial documents to ensure they are acceptable to patients with amendments made accordingly.

The TIPAL trial team will identify and appoint patient and public involvement representatives for each of the TMG and TSC. Their input will be used to guide the undertaking of the research as and where appropriate.

The results of the trial will be discussed with the representatives prior to submission of any formal reports.

8 Ancillary Studies

The TIPAL SWAT will be outlined separately

9 Protocol Amendments

Protocol Version	Date	Summary of Changes
v1.1	31/03/2020	The majority of amendments were minor and made in response to the comments received following review by the Research Ethics Committee. The following changes were made in addition to those requested by ethics: • Addition of REC and ISRCTN reference numbers • Update of DMC composition • References to IMP as tablets replaced with capsules • Clarity added to section 6.11.2. • Amendment of severity assessments for consistency with AE coding system • Update of table numbers • References updated
V1.2	21/05/2020	Amendments made relate solely to the notice of non-acceptance correspondence received from the MHRA: • Correction to exclusion criteria 6 and 9 • Updates to section 6.11 to ensure all serious adverse events are reported to NCTU
V2.0	18/08/2020	Amendments and updates required to ensure trial remains deliverable in the post-COVID19 setting: • Update of scientific query postal address (section 1.3) • Amendment of exclusion criterion 1 to exclude participants unable to complete study assessments (sections 1.3 and 6.3.1.3) • Update of date of first enrolment (section 1.3) • Addition of secondary outcome to assess laboratory FVC and FEV1 values where available (section 1.3 and 6.5.2) • Modification of the definition of disease free progression to remove DLCO measurement and confirmation that progression will be assessed from the date of randomisation to the week of the progressive event (section 1.3, 6.5.2 and 6.10.4.1) • Addition of a secondary outcome assessing the decline and rate of decline in FVC (section 1.3, 6.5.2 and 6.10.4.1) • Update to protocol contributors and Sponsor and trial team personnel (sections 1.4.1 – 1.4.3) • Trial diagram (figure 1) updated (section 2)

		• Update to protocol abbreviations (section 3) • Addition of 'primary outcome data collection' sub-section (section 5.1) • Amendment to allow all study visits to be conducted in person at recruiting sites or remotely (section 6.1.1 and 6.6.1.1) • Explanation of screening assessments related to domiciliary spirometry (section 6.3.1.1) • Clarification that FEV1/FVC ratios reviewed during screening should be assessed from most recent spirometry assessments recorded in patient medical notes (section 6.3.1.3) • Clarification that participants unwilling or unable to continue to complete study assessments may be withdrawn (sections 6.4.7, 6.6.3 and 6.10.3) • Schedule of Assessments (figure 2) updated (section 6.6) • Screening visit updated to include shipping of study supplies kit (section 6.6.1.2) • Permit safety blood tests to be taken at participants GP surgery for all study visits (sections 6.6.1.3, 6.6.1.5, 6.6.1.6 and 6.6.1.8) • Permit the use of domiciliary spirometry to capture the primary endpoint (throughout protocol) • Permit participant fitting and initiation of cough and activity monitors with remote support from research team (sections 6.6.1.3 and 6.6.1.5) • Provision of freepost envelopes for participant's opting to complete paper based questionnaires remotely (section 6.6.1.5, 6.6.1.6 and 6.6.1.8) • Permit adherence assessments based on participant confirmation of number of remaining capsules (sections 6.6.1.6 and 6.6.1.8) • Clarification that 0, 1 or 2 blood samples for research purposes may be taken from participants and that genotype samples may not be taken from consenting participants in the event that they do not attend a study visit in person (section 6.6.2) • Sample size calculation justification relative to domiciliary spirometry (section 6.7) • Permit electronic informed consent (section 6.8.1 and 7.5) • Permit remote informed consent (section 6.8.1) • Update to participant retention strategies (section 6.8.2) • Update to the data management requirements to undertake this study using remote capture of measurements (sections 6.10.1 and 6.10.2) • Addition of recording positive COVID-19 infections (section 6.10.1) • Central monitoring of domiciliary spirometry (section 6.12.3.2)

		• Clarification and update to collection of identifiable data (section 7.6) • Clarification that laboratory lung function assessments will be conducted where possible (throughout protocol) In addition to the above, minor administrative, typographical and formatting changes have been made throughout the protocol. The reference list has also been updated where relevant and required.

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11 Appendices

None.

12 Principal Investigator compliance statement

All TIPAL PI's are required to sign a site specific copy of the investigator compliance statement below prior to activation.

Principal Investigator agreement to confirm adherence to the protocol, the UK Policy Framework for Health and Social Care Research and GCP.

TIPAL

The effectiveness and risks of **T**reating people with **I**diopathic **P**ulmonary fibrosis with the **A**ddition of **L**ansoprazole (TIPAL): a randomised placebo-controlled multi-centre clinical trial

Trial protocol version	[insert current version number]
Trial protocol date	[insert date of current version]

I, [Insert investigator name], confirm:

1. that [insert name of site] site is willing and able to comply with the requirements of the TIPAL trial;
2. that I regularly treat the target population and believe the site has the potential for recruiting the required number of suitable subjects within the agreed recruitment period (figures included in the trial recruitment plan);
3. that I have sufficient time to properly conduct and complete the trial within the agreed trial period;
4. that I have supplied an up to date curriculum vitae, GCP certificate and/or other relevant documentation requested by NCTU, to demonstrate that I am qualified by education, training and experience to assume responsibility for the proper conduct of the trial at this study site;
5. that I am thoroughly familiar with the appropriate use of the investigational products as described in the protocol, in the current SPC, in the product information and in other information sources provided by NCTU;
6. that I have an adequate number of qualified staff and adequate facilities available for the foreseen duration of the trial to conduct the trial properly and safely;
7. that I will maintain a signature and delegation log of appropriately qualified persons to whom I have delegated trial related duties which includes confirmation that each member of staff is appropriately trained (including GCP) for the roles allocated to them, and will ensure this is made available to NCTU in a timely manner on request;
8. a research CV for each member of staff on the delegation log will be stored in the site file according to site policy;
9. that I take responsibility for ensuring all staff delegated trial related duties are adequately informed about the protocol, the investigational product and their trial related duties and

functions, and that I will continue to take responsibility for regularly updating them as new information becomes available;

10. that the [insert name of site] site has sufficient resources to manage data generated by the trial to allow prompt and complete data and query return to NCTU;
11. that I am aware of, and will comply with, the principles of GCP as given in the TIPAL protocol compliance statement and the applicable regulatory requirements, and that a record of my GCP training is accessible and described on my current curriculum vitae;
12. that a record of GCP training is accessible for all staff delegated responsibilities in relation to the TIPAL trial and who are named and approved on the site signature and delegation of responsibilities log and that individual training evidence will be saved in the site file, for all staff, according to trust policies;
13. that I will permit routine and for-cause monitoring and auditing by NCTU, and inspection by the appropriate regulatory authorities, including the provision of direct access to source data and other participant notes and files as required; and
14. that I agree to archive and/or arrange for secure storage of TIPAL trial materials and records for a minimum of 5 years after the close of the trial unless otherwise advised by the NCTU.

Agreement: Principal Investigator

Name	[insert name]
Signature	[insert wet signature]
Date	[insert date]

Please return a copy of this signed agreement (to the NCTU trial team at *tipal@uea.ac.uk)*.