Docusign Envelope ID: A6DAC8E8-6F10-4327-8025-E1CD958A804C

Full title: A multi-centre double-blind randomised placebo-controlled group-sequential superiority trial to assess the effectiveness and cost-effectiveness of oral **C**orticosteroids in patients wit**H** fibr**O**tic hype**R**sensitivity pne**U**moniti**S**

Short title: Testing oral corticosteroids for the treatment of fibrotic hypersensitivity pneumonitis: the CHORUS Trial

PROTOCOL;

Version v2.0 28th January 2025

IRAS number:	**1010739**
ISRCTN:	**58111563**
Funder's reference:	**NIHR155220**
Sponsor's reference	**2409609**

This protocol has regard for the HRA guidance

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i. SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: DocuSigned by: EF9FA00DF8A9463...	Date (dd/mm/yyyy): 02 April 2025 | 02:32 PDT
Name (please print): Alison Kerridge	
Position: RDUH Sponsor Manager	

Chief Investigator:

Signature: DocuSigned by: Michael Gibbons E46F5C80A7CB479...	Date (dd/mm/yyyy): 26 March 2025 | 06:05 PDT
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Signature: Signed by: Clare Griffin 08AFCEB73AD34A8...	Date (dd/mm/yyyy): 26 March 2025 | 12:15 GMT
Name: (please print): Clare Griffin	

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ii. PROTOCOL AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A. Response to initial submission REC feedback	2.0	N/A	Lucy Tregellas	Updates made in response to REC feedback: • Section 7.9: clarification that participants who lose capacity will be withdrawn from the trial • Section 7.10.2 clarification that blood samples will be stored for 15 years and then destroyed • Section 12.5: clarification that anonymised CT scans, will be stored indefinitely along with the anonymised dataset

iii. KEY TRIAL CONTACTS

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Funder	This study/project is funded by the NIHR HTA Programme (NIHR155220). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care
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v. LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CONSORT	Consolidated Standards Of Reporting Trials
CTA	Clinical Trial Authorisation
DLco/ TLco	Total Diffusing Capacity of Carbon Monoxide
DMC	Data Monitoring Committee
DMP	Data management plan
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
ExeCTU	Exeter Clinical Trials Unit
FEV1	Forced Expiratory Value
FHP	Fibrotic Hypersensitivity Pneumonitis
FBC	Full Blood Count
FVC	Forced vital capacity
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
HEAP	Health Economics Data Analysis Plan
HPDE	High Density Polyethylene
HRA	Health Research Authority
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
ILD	Interstitial Lung Diseases
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IMP-MS	Investigational Medicinal Product Management System
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
LFT	Liver Function Tests
L-PF	Living with Pulmonary Fibrosis
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence

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NIHR	National Institute for Health and care Research
NIHR RDN	NIHR Research Delivery Network
NHS R&D	National Health Service Research & Development
PAG	Patient Advisory Group
PGI-S	Patient Global Impression of Severity
PI	Principal Investigator
PIS	Participant Information Sheet
PFT	Pulmonary Function Tests
PROM	Patient Reported Outcome Measures
PSF	Pharmacy site file
RCT	Randomised Control Trial
REC	Research Ethics Committee
RUQ	Resource Use Questionnaire
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
U&Es	Urea & Electrolytes
VAS	Visual Analogue Scale
WI	Work Instruction

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vi. TRIAL SUMMARY

Trial Title	A multi-centre double-blind randomised placebo-controlled group-sequential superiority trial to assess the effectiveness and cost-effectiveness of oral Corticosteroids in patients witH fibrOtic hypeRsensitivity pneUmonitiS	
Short title	CHORUS	
Clinical Phase	Phase 3	
Trial Design	Double-blind, randomised (1:1) placebo-controlled, multi-centre, group-sequential, superiority trial, with internal pilot phase and parallel health economic evaluation.	
Trial Participants	Adults diagnosed with fibrotic hypersensitivity pneumonitis (FHP) within the last 6 months, and not previously/currently treated for FHP with prednisolone.	
Planned Recruitment Target	222	
Treatment Duration	26 weeks + 9 week weaning period	
Follow-up Duration	26 weeks from randomisation	
Planned Trial Period	48 months: M1 to M9 Trial set-up M10 to M34 Participant recruitment (including internal pilot phase) M14 to M41 Follow up M42 to M48 Analysis and write-up	
	Objectives	Outcome Measures
Primary	Assess the effectiveness of 26 weeks of treatment with prednisolone versus (vs) placebo, on disease progression, using force vital capacity (FVC)	Change in absolute forced vital capacity (FVC) (measured using the pulmonary function test) from baseline to 26 weeks post-randomisation
Secondary		
	Assess effectiveness of prednisolone vs placebo on disease progression at 12 weeks post-randomisation using: A. FVC	A i) Change in absolute FVC from baseline to 12 weeks post-randomisation A ii) Percentage change in FVC from baseline to 12 weeks post-randomisation A iii) Absolute change in percentage predicted FVC from baseline to 12 weeks post-randomisation
	Assess effectiveness of prednisolone vs placebo on disease progression at 26 weeks post-randomisation using: A. FVC B. Diffusion Co-efficient for carbon monoxide (DLco)	A i) Percentage change in FVC from baseline to 26 weeks post-randomisation A ii) Absolute change in percentage predicted FVC from baseline to 26 weeks post-randomisation B i) Absolute change in DLco (recorded using the European

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		Respiratory Guidelines) from baseline to 26 weeks post-randomisation B ii) Percentage change in DLco from baseline to 26 weeks post-randomisation B iii) Absolute change in percentage predicted DL_{CO} from baseline to 26 weeks post-randomisation
	Assess initiation of antifibrotic therapy / additional immunosuppressive therapy during the 26-week treatment window	i) Initiation of antifibrotic therapy given by 26 weeks post-randomisation ii) Additional immunosuppressive therapy given by 26 weeks post-randomisation window
	Assess effect of prednisolone vs placebo on participant-reported outcome measures (PROMs) of quality of life, including disease-specific quality of life measures, at baseline, week 12 and week 26	Changes from baseline to (i) 12 and (ii) 26 weeks post-randomisation measured using: • EQ5D-5L Health-Related Quality of Life Questionnaire • Living with Pulmonary Fibrosis (L-PF) Questionnaire (dyspnoea, cough and fatigue domain scores of principal interest) • Cough Visual Analogue Scales (VAS) • Global rating of change (Patient Global Impressions – Severity (PGI-S) scale)
	Assess safety of prednisolone	Safety data will be collected in accordance with MedDRA. Specific events of interest are: • Adverse reactions • Respiratory hospitalisations • Acute exacerbations • Weight gain/ increased waist circumference • Adverse events of special interest- infections (see section 9.3) • Death
	Assess health/social care service resource use	Health/social care Resource Use Questionnaire collected at baseline, 12 and 26 weeks post-randomisation
	Assess cost-effectiveness of prednisolone vs placebo over 26 weeks of treatment	Health economic evaluation via collection of data at baseline, 12 and 26 weeks post-randomisation using the EQ5D-5L and Resource Use Questionnaire
Investigational Medicinal Product(s)	Prednisolone (and matched placebo)	

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Formulation, Dose, Route of Administration	Oral prednisolone or matched placebo capsules. Starting at 40mg/day, titrated to 10mg/day maintenance dose by Week 12 and continue 10mg/day until Week 26. Then gradually weaned off by week 35 (see trial treatment section 8.0).

vii. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
The NIHR HTA	Funding the trial in its entirety.
Qureight Ltd 50 - 60 Station Road Cambridge CB1 2JH United Kingdom Company reg #11132399	Qureight, Ltd. are storing the pseudonymised CT scans free of charge.

viii. ROLE OF TRIAL SPONSOR AND FUNDER

Sponsor role

Royal Devon University Healthcare NHS Foundation Trust is Sponsor for the CHORUS trial. The Sponsor has input into the design of the trial and the drafting of this protocol but overall responsibility for the design lies with the Chief Investigator (CI). The Sponsor is responsible for authorising the initial submission to the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC) and Health Research Authority (HRA) and any subsequent amendments. The Sponsor will ensure appropriate agreements and indemnity arrangements are in place, overseeing the conduct of the trial and ensuring it adheres to the principles of Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research. The Sponsor will oversee archiving at the end of the trial. The Sponsor is not responsible for and has no involvement in the data analysis or interpretation, or for writing manuscripts.

Funder role

The NIHR as funder are responsible for providing funds to cover the agreed research costs. The funder is not responsible for and has no involvement in data analysis or interpretation, or for writing manuscripts.

Clinical Trials Unit role

Exeter Clinical Trials Unit (ExeCTU), University of Exeter, is the Clinical Trials Unit responsible for the day-to-day management of the trial. Responsibilities of ExeCTU, the Sponsor and CI are defined in detail in a separate task allocation document. ExeCTU will be closed on bank holidays and University of Exeter closure days.

ix. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Steering Committee

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The Trial Steering Committee (TSC) will comprise an independent chairperson with expert knowledge in the subject area, an independent statistician, an independent health economist, Patient and Public Involvement (PPI) representative(s) and at least one other independent professional member. The CI and co-lead will join the TSC as non-independent members. Observers will be invited to attend TSC meetings but will not be voting members (e.g. trial manager(s), trial statistician(s), health economist(s), Sponsor representative, Funder representative).

The role of the TSC is to monitor and supervise the progress of the trial. The TSC chair and/or TSC committee will have reviewed the final protocol prior to the trial opening to recruitment and the TSC independent statistician will approve the Statistical Analysis Plan (SAP) prior to final database lock. The TSC will meet prior to recruitment commencing and approximately 6-monthly thereafter. Further details of the roles and responsibilities of the TSC are documented in the TSC charter.

Data Monitoring Committee

The Data Monitoring Committee (DMC) will comprise three independent professional members, including an independent statistician. The CI, co-lead, senior statistician, trial statistician and trial manager will be invited to attend the open sessions of DMC meetings but will not be voting members. The senior statistician will be unblinded throughout the trial and attend the closed sessions of DMC meetings.

The DMC will monitor accumulating trial data, including safety, interim analyses and make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or early closure of the trial. Further details of the roles and responsibilities of the DMC are documented in the DMC charter.

Trial Management Group

The Trial Management Group (TMG) will be composed of the CI, co-lead, trial co-applicants, trial statisticians, trial health economists, PPI lead, at least one lay representative, the trial manager(s), data manager(s) and a Sponsor representative. The TMG is responsible for writing the protocol and participant-facing materials, obtaining relevant approvals from an NHS REC, the MHRA and the HRA, coordinating with NHS Trusts to set up sites, reviewing the statistical analysis plan and ensuring the trial is conducted according to the principles of GCP and the UK Policy Framework for Health and Social Care. The TMG will meet regularly (approximately every month) to manage the trial, monitor safety, key performance indicators and discuss and resolve emerging issues. Members of the TMG will analyse the data, interpret the analyses, write reports to the funder and write and submit manuscripts to peer-reviewed journals.

PPI group

An overarching Patient Advisory Group (PAG), led by the PPI lead, will have reviewed patient-facing materials prior to submission for ethical review and will have input into any revisions to patient-facing materials throughout the trial. This group will meet regularly throughout the trial. The PPI work will be led by Action for Pulmonary Fibrosis, a charity organisation dedicated to supporting people with all types of pulmonary fibrosis and have extensive experience of supporting research projects.

x. Key words

Respiratory, prednisolone, corticosteroids, pulmonary fibrosis, hypersensitivity pneumonitis, randomised trial, placebo-controlled, double-blinded

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xi. TRIAL FLOW CHART

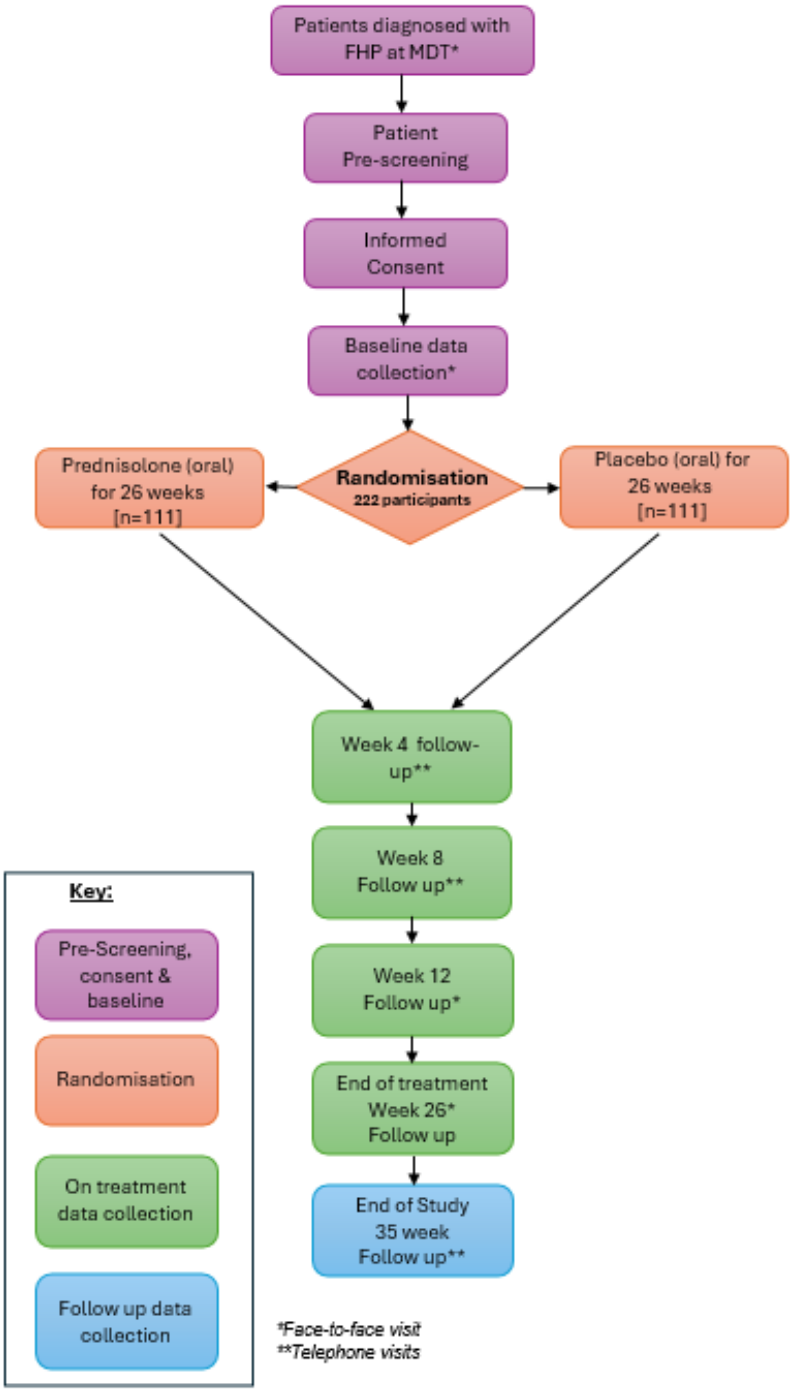

Figure 1 Participant pathway

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1. BACKGROUND

Fibrotic hypersensitivity pneumonitis (FHP) is a devastating and debilitating lung disease. Median survival from diagnosis is only 5 years, similar to many deadly cancers [1, 2]. FHP causes significant morbidity and mortality [3], with inexorable deterioration in breathlessness, cough and quality of life, with patients becoming housebound and dependent on oxygen. FHP is the most common subtype within the group of lung conditions termed “progressive pulmonary fibrosis” (PPF), accounting for a third of PPF cases in the UK [4]. PPF, including FHP, are interstitial lung diseases (ILD): lung disorders characterised by variable amounts of inflammation (potentially reversible) and fibrosis (progressive scarring, irreversible) of the lung parenchyma (tissue). FHP is more common in people aged over 65 years (up to 11 per 100,000) [3]. Incidence is rising and there are an estimated 2000 new cases per year in the UK. The death rate due to FHP in the UK is unknown but PPF is believed to account for up to 2% of all UK deaths annually.

Historically it was believed that FHP was less severe/progressive than idiopathic pulmonary fibrosis (IPF). However, recent data from the Canadian Registry for Pulmonary Fibrosis [5] identifies FHP as almost identical to IPF in its progressive nature, and that FHP is more severe/progressive than all the other ILDs. FHP is believed to be an immune-mediated disease [1] and as such corticosteroids, such as prednisolone, are commonly used to treat this patient group. However, there remains an absence of evidence to support the use of corticosteroids for FHP [1, 6, 7] despite their numerous potential side effects [8].

Literature and clinical trial registries were searched to 2023 (Medline: “steroids” AND “chronic hypersensitivity pneumonitis” OR “fibrotic hypersensitivity pneumonitis” OR “chronic farmer’s” OR “chronic extrinsic allergic” OR "chronic pigeon" OR "chronic bird"; the latter terms were included as these are common exposures with increased risk for FHP). The benefits of corticosteroids on pulmonary function in acute, non-fibrotic, hypersensitivity pneumonitis (HP) were supported by a single, small, randomised controlled trial (RCT) of 36 patients, where pulmonary function improved after 1 month of treatment, but with no longer-term effect (assessed at 5 years); no data was collected on safety or cost-effectiveness [9]. No randomised controlled trials (RCT) (placebo-controlled) assessing corticosteroid therapy on outcomes in FHP have been reported. A cohort of HP patients treated with immunosuppressive therapy was described in a retrospective trial [10]. Forty-one patients were treated with prednisolone monotherapy and had an average decline in pulmonary function (as measured by forced vital capacity, FVC) of 10% over 36 months compared to an average decline of 1.3% in 38 patients who were not treated, suggesting prednisolone may be detrimental. However, untreated patients had significantly higher FVCs at baseline, making it difficult to draw direct comparisons. In a single-centre trial, a retrospective cohort of 109 HP patients was described, of whom 82 received corticosteroid treatment [11]. Treatment had no effect on monthly rate of decline of FVC. There was a trend towards worse survival in the corticosteroid-treated patients, although this was no longer seen when the analysis was adjusted for age, gender, and baseline FVC. More recently, a retrospective review was undertaken of 144 patients with FHP [12]. A propensity score-matched analysis of 60 patients, without extensive fibrosis, identified that those treated with prednisolone (throughout the observation period) had significantly better FVC at 6, 12, and 24 months. The authors proposed early initiation of corticosteroids should be considered for FHP patients. A retrospective review of 93 HP patients (including 54 with FHP) [13] noted improvements in 19 (35%) cases with FHP, while overall, fibrosis on high-resolution computerised tomography scanning was associated with a worse prognosis. It was concluded that future trials examining the role of immunosuppressive treatments are urgently required.

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It is important to also consider whether immunosuppression in FHP may be detrimental, as previously observed in IPF. The NIH-funded PANTHER trial [14] demonstrated that combination immunosuppressive therapy was hazardous in patients with IPF: a planned interim analysis revealed that those in the combination therapy group (prednisolone/azathioprine/N-acetyl cysteine, standard care for IPF [15] prior to the trial) had an increased rate of death (10% vs. 1%, p=0.01) and hospitalisation (30% vs. 9%, p<0.001) compared to placebo. However, it is now believed that IPF (unlike FHP) has no significant inflammatory component [16]. This was not clear when the PANTHER trial was designed [17].

Furthermore, the dose of corticosteroids used in PANTHER was higher than that proposed in this trial (prednisolone approximately 22.7mg/day over 26-week period for an 80kg individual in PANTHER trial versus 17.5mg/day in CHORUS) [14], and we intend to use single agent immunosuppressive therapy as opposed to the combination therapy used in the PANTHER trial (prednisolone plus azathioprine plus N-acetyl cysteine).

Despite the paucity of evidence to support, or refute, the use of steroids in FHP, clinicians regularly prescribe this treatment. We have designed this trial together with patients, carers, and the public to address this knowledge gap and patient need.

2. RATIONALE

While a recent international guideline has been published to aid standardisation of the diagnosis of FHP [17], there are no guidelines (national or international) to assist with subsequent clinical management. The lack of an evidence-based approach to the management of FHP, together with the need for high-quality RCTs, has been widely discussed [1, 11, 18]. The most recent international expert statement regarding management of FHP (2017) is based on observational data and expert opinion [1]; it states that a trial of immunosuppression should be considered, with the aim of reducing/reversing the inflammatory component of FHP. The Great British HP survey (GBHP Survey, 2018) [19] sought to gather information on the real-life management of FHP. It identified that FHP was treated with immunosuppressive therapy by 94% of responding respiratory specialists, with median peak dose of prednisolone of 40mg, with a median therapy duration of 1.5 months (range 0-6 months). Long-term (>1 year) maintenance prednisolone was commonplace (median dose 10.4mg, range 0-40mg). Whilst the majority of clinicians treated FHP patients with immunosuppressive therapy, 61% reported concerns this may increase mortality risk. Data from the Canadian Registry for pulmonary fibrosis [5] demonstrated that 49% of patients with FHP were treated with some form of immunomodulatory therapy. The true incidence and severity of adverse effects of steroids in people with FHP are unknown and therefore incidence and outcomes need to be measured. Potential adverse effects of prednisolone are listed in the British National Formulary [8].

The CHORUS trial will allow us to assess the benefits, or otherwise, of corticosteroids in the management of FHP and assess their cost-effectiveness, whilst enabling systematic collection and analysis of any potential detrimental effects/harms. The trial flow chart is summarised in Figure 1.

Evidence explaining why this research is needed now

Despite high morbidity and mortality in FHP, there remains no clinical guidelines or evidence-based treatment. Progressive pulmonary fibrosis (PPF) was the recent focus of an NIHR/James Lind Alliance Priority Setting Partnership (of which co-applicants MG and AMR NIHR155220 4 were partners) with the top 10 priorities for research published in 2022 [20]. Seven of these priorities are addressed by this trial. In addition, a recent Australian Research Priority Setting exercise identified 39 research questions; our trial aims to address six of the top 10 [21].

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The CHORUS trial is formally and strongly supported by the British Thoracic Society, following review by their Science & Research Committee.

2.1. Assessment and management of risk

FHP is commonly treated with prednisolone in secondary and tertiary care settings. The trial population and safety monitoring procedures in place in this trial are reflective of the summary of product characteristics (SmPC) and clinical experience. Mechanisms to detect and address adverse events are in place, according to established ExeCTU procedures (see pharmacovigilance section 9).

From an IMP perspective, this trial has been characterised as Type A, no higher risk than standard medical care as the investigational medicinal product (IMP) prednisolone has marketing authorisation and is currently being used widely in standard clinical care for FHP throughout the UK. Investigators will be instructed to give participants standard clinical advice on the assumption that they will be taking steroids.

Due to the precautions outlined in the SmPC, potential participants with contraindications to prednisolone will be excluded from the trial. This will exclude patients with an active infection, ocular herpes simplex or any known hypersensitivity to the active substance or any of the excipients. Blood tests will be carried out to confirm the potential participant does not have evidence of kidney failure or liver cirrhosis (Child-Pugh class B or C) prior to being randomised. A concomitant medication review must be completed at baseline prior to randomisation to ensure the patient is not receiving any antibiotics for an active infection and is not taking any of the contraindicated medications as outline in section 8.9.

All pregnant or breast-feeding patients will be excluded from the trial (see section 8.10) Participants of childbearing potential will be asked to take a highly effective method of contraception for the duration of the trial (35 weeks) and a pregnancy test at baseline. If a participant becomes pregnant during the trial ExeCTU must be notified via the pregnancy eCRF in REDCap (see section 9.6).

The risk versus benefit to participants of being on the placebo IMP is unknown as such a trial has not been conducted in this population previously. This trial aims to answer that question. Participants allocated to receive placebo could be at risk of disease progression, but it is not known if the risk is any higher than in the prednisolone group. Regular monitoring of all trial participants with telephone calls and in-person follow-up visits with the clinical team, will ensure that any safety concerns and disease progression are identified quickly. Clinicians will be able to offer second and third line therapies to participants at their discretion if in their medical judgement the participant’s disease is progressing and they could benefit from further treatment. A potential benefit of taking the placebo is not being at risk of the side effects from taking prednisolone.

All participants will be provided with contact details of the healthcare team responsible for their trial treatment at their local hospital so as they can get in touch with any concerns between scheduled trial telephone calls and follow-up visits. If necessary, participants will be invited to the hospital for an unscheduled visit if their condition deteriorates or they experience significant side effects.

The potential risks associated with prednisolone (side effects) and with placebo will be clearly described in the participant information sheet (PIS) to enable potential participants to make an informed choice about taking part in the CHORUS trial. Patients with known but controlled

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diabetes have been advised to closely monitor their blood sugar levels as prednisolone can increase blood sugar levels. Patients with poorly controlled diabetes will be excluded from the trial. The PIS will be supplemented by discussion between a medical doctor working on the trial and members of the research team at the site (e.g. research nurse, clinical research practitioner) who will be required to describe the trial in detail and answer all queries from the potential participant before taking informed consent. The person taking consent will be trained to check the patient's understanding of the trial before obtaining consent.

Prolonged administration of prednisolone can result in adrenal suppression and abrupt withdrawal could result in acute adrenal insufficiency. To minimise this risk all randomised participants will follow a weaning schedule at the end of the trial treatment period to slowly reduce their dose before stopping the trial treatment (see section 8.6.1)

Randomised participants will also be given a steroid and clinical trial participation alert card to present to any healthcare professional if they require any type of treatment for the duration of their time on the trial. The alert card will state that the participant may be taking steroids and that they cannot suddenly stop taking them, along with details of how to contact the research team at the hospital who are responsible for the participant and how to access support for emergency unblinding (see blinding section 7.7.1).

If the participant wishes to stop taking the IMP or discontinues the IMP early due to adverse events it is still advised that participants follow a weaning schedule (see section 7.9.1). Participant is made aware of this in the PIS and consent form.

A detailed risk assessment carried out by ExeCTU and reviewed by the Sponsor and TMG will be maintained and updated throughout the trial and will be used to inform the trial monitoring plan.

3. OBJECTIVES AND OUTCOME MEASURES

3.1. Primary objective

To assess the effectiveness of 26 weeks of treatment with prednisolone vs placebo on disease progression, as measured by the pulmonary function test, forced vital capacity. The change in absolute forced vital capacity (FVC) between baseline and 26 weeks post-randomisation will be compared in patients recently diagnosed with fibrotic hypersensitivity pneumonitis (FHP) and treated with daily prednisolone vs placebo.

FVC is the gold standard primary outcome measure in pulmonary fibrosis studies. FHP patients understand this outcome, it is routinely measured in clinic and used to explain the trajectory of their condition.

3.2. Secondary objectives

- Assess effectiveness of prednisolone vs placebo on disease progression at 12 weeks post-randomisation on FVC
- Assess effectiveness of prednisolone vs placebo on disease progression at 26 weeks post-randomisation on (a) FVC, (b) Diffusion Co-efficient for carbon monoxide (DLco)
- Assess initiation of antifibrotic therapy and/or additional immunosuppressive therapy during the 26-week treatment period
- Assess effect of prednisolone vs placebo on participant-reported outcome measures (PROMs) of quality of life, including disease-specific quality of life measures, at baseline, week 12 and week 26 post-randomisation

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- Assess safety of prednisolone
- Assess health/social care service resource use
- Assess cost-effectiveness of prednisolone vs placebo over 26 weeks of treatment

3.3. Outcome measures

3.3.1. Primary outcome

Absolute FVC, measured in millilitres (ml), will be recorded using the pulmonary function test (PFT), at 26 weeks post-randomisation. The primary outcome is change in absolute FVC between baseline and 26 weeks post-randomisation.

3.3.2. Secondary outcomes

1. Absolute FVC, measured in millilitres (ml) will be recorded using the pulmonary function test (PFT) at 12 weeks post-randomisation, and used to calculate change in absolute FVC between baseline and 12-weeks post-randomisation.
2. Percentage change in FVC will be calculated (using the absolute FVC values collected at baseline, 12 and 26 weeks post-randomisation) between (i) baseline and 12 weeks and (ii) baseline and 26 weeks post-randomisation.
3. Absolute change in percentage predicted FVC will be calculated between (i) baseline and 12 weeks and (ii) baseline and 26 weeks post-randomisation, using percentage predicted FVC calculated centrally by ExeCTU using Global Lung Initiative (GLI) reference equation.
4. Absolute DLco, measured in mmol min^{-1} kPa^{-1}, will be recorded using the European Respiratory Society (ERS) guidelines, at baseline and 26-weeks post-randomisation and used to calculate change in absolute DL_{CO} between baseline and 26 weeks post-randomisation.
5. Percentage change in DLco will be calculated (using the absolute DLco values collected at baseline and 26 weeks post-randomisation) between baseline and 26 weeks post-randomisation.
6. Absolute change in percentage predicted DLco will be calculated between baseline and 26 weeks post-randomisation.
7. Initiation of antifibrotic therapy given by 26 weeks post randomisation.
8. Additional immunosuppressant therapy given by 26-weeks post-randomisation.
9. Quality of life will be measured at baseline, 12 and 26 weeks post-randomisation. Changes in quality of life from (i) baseline to week 12 and (ii) baseline to week 26 will be measured using
    - L-PF questionnaire [22] (dyspnoea, cough and fatigue domain scores of principal interest)
    - PGI-S scale [23]
    - the cough VAS [24]
    - EQ-5D-5L – Visual Analogue Scale [25]
10. Safety data will be collected in accordance with MedDRA and defined as the number and proportion of participants experiencing Serious Adverse Events (SAEs) and

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related Adverse Events (AEs) throughout the duration of the trial. Specific events of interest are:

- adverse reactions
- respiratory hospitalisations
- acute exacerbations
- weight gain/increased waist circumference (percentage change)
- adverse events of special interest- infections (listed in section 9.3)
- death

11. Health/social care resource use will be assessed at baseline and 12 week and 26 week post-randomisation using a participant report Resource Use Questionnaire.
12. Cost-effectiveness will be assessed via EQ-5D-5L and Resource Use Questionnaire data collected at baseline, 12 and 26 weeks post randomisation.

3.4. Exploratory endpoints/outcomes

There are no exploratory outcomes being investigated in this trial.

4. TRIAL DESIGN

This is a prospective, two-arm, double-blind, phase III, placebo-controlled, multi-centre, group-sequential, superiority trial, in adult patients with fibrotic hypersensitivity pneumonitis. Participants will be randomised 1:1 via block randomisation. The trial includes an internal pilot phase, a single planned formal interim analysis (encompassing a blinded sample size re-estimation) and a parallel health economic evaluation.

4.1. Internal pilot and progression criteria

Judgement of the success of the internal pilot phase, assessed 12 months after the first participant is randomised, will focus on the opening of an initial 15 sites (although opening of the remaining sites will continue at pace during the latter phases of the internal pilot phase), the recruitment rate/site/month and the total number of participants recruited in the first 12 months. The figures included in Table 1 below, allow for staggered site opening.

Table 1: Internal pilot phase progression criteria

	Green	Amber	Red
% threshold	*100%*	*65% to 99%*	*<65%*
Number of sites open to recruitment*	≥15	10 to 14	<10
Mean recruitment rate/site/month**	≥0.4	0.26 to 0.39	<0.26
Total number of participants recruited*	≥50	32 to 49	<32
Trial recruitment % vs target	100%	65% to 99%	<65%
Percentage of participants remaining blinded to treatment during intervention period***	100%	90-99%	<90%

* Allowing for staggered site opening

**Calculated over months a site is open to recruitment

***Assessment of contamination from all clinically necessary unblinding

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Green: Refinements to enhance recruitment, adherence and retention will be implemented by the trial team in collaboration with local sites/R&D teams and NIHR Research Delivery Network (RDN) staff where necessary. The Funder will make the final decision as to whether the trial will continue.

Amber: The trial team, including PAG members, will discuss modifications to improve recruitment and adherence. The CI, co-lead and co-applicants will increase engagement with local sites/R&D teams to discuss emerging barriers and provide support. The CI, co-lead and co-applicants will engage directly with NIHR RDN to optimise recruitment – this will include the NIHR Respiratory National Speciality Group Lead, NIHR Respiratory Regional Clinical Research Leads, NIHR Respiratory Regional Deliver Managers, and may also include NIHR LCRN (Regional) Chief Operating Officers and Clinical Directors. The Funder will make the final decision as to whether the trial will continue.

Red: The trial team, including PAG members will discuss any mitigating circumstances with the Trial Steering Committee, Sponsor and Funder. Urgent calls will be arranged. The Funder will make the final decision as to whether the trial will continue.

4.2. Main trial

Whilst the internal pilot phase aims to open a minimum of 15 sites, opening of the remaining (projected further 15) sites will continue throughout the latter period of the internal pilot phase. On progressing to the main trial period, additional sites may be sought if required, based on the observed recruitment rates during the internal pilot phase, to reach the overall recruitment target within the planned 25-month recruitment window.

There is a planned, separate, interim analysis after the first 100 participants reach the 26-week primary endpoint, encompassing a review of the pooled standard deviation of the primary outcome (with opportunity for blinded sample size re-estimation if indicated) and a single interim analysis for effectiveness (see sample size and data analysis in section 10.1).

5. TRIAL SETTING

222 participants will be randomised from secondary and tertiary NHS care centres in England, Wales and Scotland. The majority of sites will be specialist ILD centres. Additional sites that offer shared care for people with FHP (in conjunction with neighbouring specialist ILD centres) will also be able to participate. All sites will treat and manage the continued care for trial participants. Each site will have a research team, with a local Principal Investigator (PI) who should be a medically qualified doctor and, research nurses/Allied Health Professionals (AHPs)/clinical research practitioner. A list of participating sites will be maintained by the trial management team and can be found within the Trial Master File (TMF).

6. PARTICIPANT ELIGIBILITY CRITERIA

To participate in the trial, a patient must meet all of the listed inclusion criteria, and none of the exclusion criteria. Eligibility waivers to inclusion/exclusion are not permitted.

6.1. Inclusion criteria

- Age ≥18 years
- ILD multi-disciplinary diagnosis of FHP within the last 6 months [17]
- % predicted FVC ≥40% at baseline (as per GLI equation [26])
- % predicted DL_{CO} ≥25% at baseline
- FEV_1/FVC ratio ≥0.7 at baseline
- >10% fibrosis on CT taken as standard of care for the MDT diagnosis*
- Able to provide informed consent

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- People of child-bearing potential** must be willing to:
  - Take a pregnancy test at baseline, before randomisation
  - Use of a highly effective method of contraception for the duration of the trial (35 weeks)***
  - Inform the research clinical team if pregnancy occurs during trial participation

** Determined visually by delegated medically qualified doctor*

*** Potential participants are considered not of child-bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or they are postmenopausal (no menses for 12 months without an alternative medical cause).*

**** Highly effective contraception is defined as one of the following: combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device(IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; practising true sexual abstinence (when this is in line with the preferred and usual lifestyle of the individual).*

6.2. Exclusion criteria

- Previous or current therapy with prednisolone or other immunosuppressive agent for FHP
- Active infection (use of antibiotics must be completed 2 weeks prior to the baseline visit. Prophylactic antibiotics are allowed)
- Emphysema>fibrosis on CT scan*
- BMI>44 kg/m^2
- Currently enrolled in another investigational drug trial
- Non-respiratory conditions requiring use of immunosuppressive therapy (including prednisolone)
- Any condition that might be significantly exacerbated by the administration of prednisolone, including but not limited to: Cushing's and Conn's Syndromes, Addison's disease, poorly controlled/difficult to control diabetes
- Patients with underlying liver cirrhosis (Child Pugh, B, or C hepatic impairment).
- Stage 4/5 chronic kidney disease (eGFR <30ml/min/1.73m^2)
- Patients with unstable cardiac disease or a significant disease or condition other than the ILD under trial, which in the opinion of the investigator, may put the patient at risk because of participation, interfere with trial procedures, or cause concern regarding the patient's ability to participate in the trial
- Use of potent inducers of prednisolone including phenytoin, rifabutin, carbamazepine, ketoconazole, rifamycins. Please refer to the Summary of Product Characteristics and concomitant medications section 8.9
- Patients with ocular herpes simplex
- Known allergy to prednisolone or its excipients including lactose anhydrous or capsule ingredients Hydroxypropylmethylcellulose, water, Dye – copper complex of chlorophyllins E141ii
- Pregnant**, breastfeeding, or planning to conceive in the next 35 weeks

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** Determined visually by delegated medically qualified doctor*
***Must have a negative pregnancy test within 7 days prior to randomisation*

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7. TRIAL PROCEDURES

Table 2: Data collection and schedule of assessments

Assessment / event	Pre-Screening (prior to approach)	Baseline (in person)[a]	Randomisation	On treatment follow up				End of Study follow up
				Week 4[b]	Week 8[b]	Week 12[a] (-14 days /+7 days)	Week 26 EoT[a] (-14 days /+7 days)	Week 35[b]
Screening log	X	X	X					
Baseline Pulmonary function measurements- spirometry (FVC, FEV1, FEV1/FVC ratio)[c]		X						
Pulmonary function measurements- spirometry (FVC)						X	X	
Pulmonary function measurements- gas transfer (DLco/TLco)[d]		X					X	
Local CT report findings	X							
Local bronchoscopy findings	X							
MDT diagnosis of FHP	X							
Informed consent		X						
Baseline bloods (FBC, U&Es, LFTs)[e]		X[f]						

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Assessment / event	**Pre-Screening (prior to approach)**	**Baseline (in person)[a]**	**Randomisation**	**On treatment follow up**				**End of Study follow up**
				Week 4[b]	Week 8[b]	Week 12[a] (-14 days /+7 days)	Week 26 EoT[a] (-14 days /+7 days)	Week 35[b]
Pregnancy test		X[g]						
Research blood sample (optional consent)		X				X		
Physical exam (BP, SO2, height, weight, waist circumference)		X						
Medical history/ comorbidities	X	X						
Concomitant medication	X	X						
Contact details		X						
Demographic data		X						
Cough visual analogue scale (VAS)		X				X	X	
Living with Pulmonary Fibrosis (L-PF)		X				X	X	
EQ-5D-5L		X				X	X	
Patient Global Impressions – Severity scale (PGI-S)		X				X	X	

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Assessment / event	**Pre-Screening (prior to approach)**	**Baseline (in person)[a]**	**Randomisation**	**On treatment follow up**				**End of Study follow up**
				Week 4[b]	Week 8[b]	Week 12[a] (-14 days /+7 days)	Week 26 EoT[a] (-14 days /+7 days)	Week 35[b]
Health and social care resource use questionnaire		X				X	X	
Previous environmental exposures for FHP		X						
Smoking and/or vaping status		X						
Weight and waist circumference							X	
Eligibility checklist			X					
Randomisation			X					
Participant reported IMP compliance						X	X	X
IMP dose modifications						X	X	
Adverse event review				X	X	X	X	X
Concomitant medication review				X	X	X	X	X
Additional therapies for FHP				X	X	X	X	X

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a. *In person IMP dispensing visits (EoT= End of study)*
b. *Telephone visits however if there any safety concerns the participant can be seen in clinic for these visits*
c. *Absolute forced vital capacity (FVC), forced expiratory value (FEV_1)*
d. *Corrected gas transfer total diffusing capacity of CO (DLco/TLco)*
e. *Full blood count (FBC), urea and electrolytes including eGFR (U&Es), liver function test (LFT)*
f. *Baseline bloods taken with 30 days prior to randomisation can be used*
g. *Only required for participants of child-bearing potential and must be negative within 7days of randomisation*

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7.1. Recruitment

Potential participants will be identified locally across UK secondary and tertiary care NHS sites. Recruitment processes will be performed by appropriately trained and delegated members of the research delivery team (e.g. medical clinician, research nurses) according to GCP. The NIHR Associate Principal Investigator Scheme will also be utilised to support recruitment.

7.1.1. Participant identification

Potentially eligible participants will primarily be identified through MDT outcomes and clinic lists. Identification may also be via local patient or research registries and hospital medical records. Research delivery teams (which make up part of the direct clinical care team), including the PI who is responsible for the clinical care of the patient, will identify patients aged 18 years and over with a diagnosis of FHP from an MDT within the past 6 months. All potentially eligible participants will be documented on the screening log electronic case report form (eCRF).

The participant recruitment pathway is summarised in Figure 2.

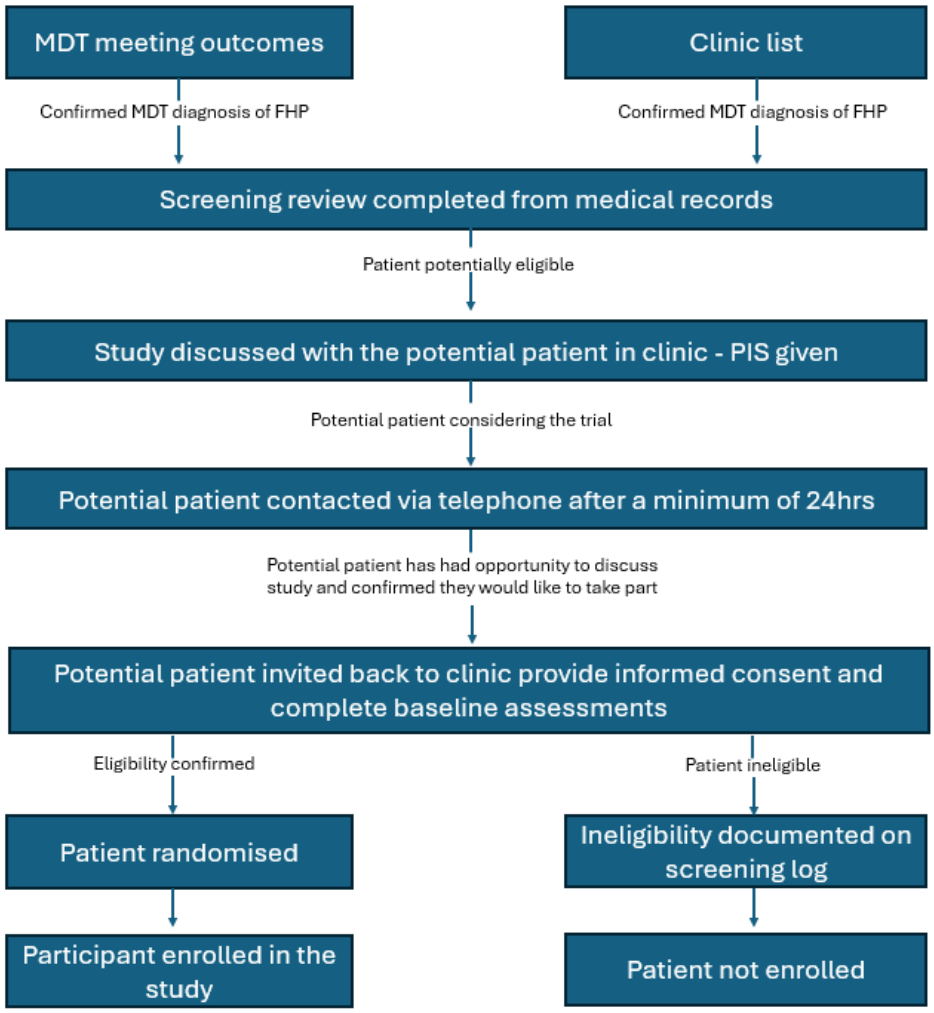

Figure 2: Participant recruitment pathway

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7.2. Pre-screening

Screening will be performed by research delivery teams (which make up part of the direct clinical care team), at each site who are trained and delegated the task by the local PI.

Screening will be conducted in two stages:

1. Pre-screening – before the potential participant is approached and informed consent obtained, based on information available in medical records (tests performed and history taken as part of standard care).
2. Post-consent, at baseline assessment visit – after the potential participant has been approached about the trial and they have given written informed consent. Blood tests and a pregnancy test (if applicable) will be carried out to confirm that the participant meets the full eligibility criteria, before they are randomised (enrolled) into the trial. (see baseline assessment section 7.5 and trial assessments section 7).

The pre-screening review will include:

- Age
- MDT diagnosis date of FHP within the last 6 months not previously treated with prednisolone
- >10% fibrosis on CT used for MDT diagnosis**
- Not known to be currently receiving any immunosuppressive therapy (including prednisolone) for any cause*
- Not known to have any significant co-morbidities or a condition that might be significantly exacerbated by the administration of prednisolone*
- Not known to have any of the following co-morbidities*:
    - Active infection
    - Liver cirrhosis Child-Pugh grade B or C
    - Stage 4/5 chronic kidney disease
    - Unstable cardiac disease
    - Emphysema>fibrosis on CT scan used for MDT diagnosis**
- Not known to have an allergy to prednisolone or any of its excipients
- Not known to be pregnant or breast feeding
- Not known to be participating in another intervention trial

*If not available at pre-screening assessment from the medical records, these must be assessed at the baseline visit after informed consent has been obtained and be checked and eligibility confirmed prior to randomisation (see baseline assessment section 7.5 and trial assessments section 7)

** Assessed visually by delegated medically qualified doctor

Following the pre-screening eligibility check, potentially eligible participants will be introduced to the trial during a routine clinic visit by the PI (or delegate) and given a PIS to take home and consider. Patients will be given a minimum of 24 hours to consider the trial. After this time a member of the research delivery team (which make up part of the direct clinical care team), will telephone the patient to establish their interest in trial participation, provide more detailed information on the trial, and answer any questions. If the patient is interested in taking part in the trial, they will be invited to a hospital appointment to obtain written informed consent and complete a baseline assessment (see Consent Section 7.4 and Baseline assessment Section 7.5 for details).

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7.2.1. Screening log

A screening log eCRF will be completed for all potentially eligible participants identified at pre-screening. Personal identifiable data will not be recorded on screening logs, instead a unique participant number will be assigned.

The screening log will collect:

- Date patient identified
- Age
- Sex at birth
- Ethnicity
- Languages spoken and if translational services were used
- Reason for not approaching/ ineligibility/ declining (if available)

7.3. Payment

A small payment will be offered to each participant at each hospital visit as a thank you to put towards travel expenses/ car parking charges. Sites will be responsible for administering reimbursement.

7.4. Informed consent

Informed consent will be sought from each potentially eligible and interested patient by an appropriately trained and delegated member of the site research team (PI, research nurse or nurse specialist, clinical research practitioner) before enrolment into the trial. Staff who take informed consent will be required to have completed GCP training within the past 3 years. Consent will be obtained face to face electronically using a purposely designed electronic consent form in the trial database (REDCap). While electronic consent is the preferred method, if for any reason, obtaining consent using REDCap is not possible (e.g. technical issues or the site or the patient prefers to use paper) informed consent can be obtained in writing on a paper consent form. The site research team will be provided with a consent work instruction which will provide detailed information on the consent process.

Whether completed electronically or on paper, the consent form will be signed by the participant and countersigned by the delegated staff member receiving consent.

As part of the consent process, participants can optionally consent to:

- Collection of their CT scans performed as standard of care and stored with a third party vendor for future research studies
- Collection of blood samples at baseline and 12 weeks to be shipped to a central laboratory and stored for future genotyping and other mechanistic work

Patients can still participate in the main trial if they decline any or all of the above optional activities.

Participants will also be asked for their preference on remaining in, or withdrawing from, the trial in the event they lose mental capacity during the trial (see section 7.9 for details)

For patients of childbearing potential, their agreed method of contraception should be discussed.

Sites should document key details of the informed consent process in the patient's medical record. Patients are not required to provide reasons if they choose not to participate, but if reasons are given, then they should also be documented in their medical notes and the trial

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screening log on REDCap. The site research team must ensure a copy of the consent form is provided to the participant either by email (participants will provide this on the eConsent form) or physical copy downloaded from REDCap printed at site and a copy given to the participant. Copies should also be added to the medical notes, stored in the ISF (or a file note to their location) and for paper consent forms only, an unredacted copy will be uploaded to REDCap by the site team, for remote monitoring by ExeCTU.

7.5. Baseline assessments and data collection

The baseline assessment visit will be conducted in person after informed consent has been provided. This can be on the same day as consent is provided, or within 7 days post-consent. Final trial eligibility will be confirmed during the baseline visit after the participant has given informed consent. A medically qualified doctor who is authorised on the delegation of duties log is responsible for confirming eligibility.

Baseline data to be collected will include:

- Contact details and contact preferences
- Demographics (including age*, sex at birth*, ethnicity*, date of birth, self-reported gender, postcode for index of multiple deprivation)
- NHS number (or equivalent)
- Vital signs/physical exam (including blood pressure, oxygen saturation, height & weight for BMI, waist circumference)**
- Pulmonary function measurements**
    - Spirometry measurements: forced vital capacity (FVC), forced expiratory value (FEV_1) and FEV_1 / FVC ratio
    - Gas transfer measurements: total diffusing capacity of carbon monoxide (DLco/TLco)
- Baseline bloods including FBC, U&Es and LFTs (bloods taken with 30 days prior to baseline visit can be used) **
- CT report details (from most recent CT done as standard of care)
- Bronchoscopy details (from most recent bronchoscopy done as standard of care)
- Smoking and vaping history/status
- Previous environmental exposures for FHP
- Full concomitant medication review to ensure eligibility (see exclusion criteria section 6.2)**
- Medical history/ comorbidities review to ensure eligibility (see exclusion criteria section 6.2)**
- Pregnancy test for participants of childbearing potential

**This data will be collected pre-consent on the screening log.*
***Must be checked and eligibility confirmed prior to randomisation, full blood count (FBC), urea & electrolytes (U&Es) and liver function tests (LFTs)*

*Questionnaires (participant completed)****

- EQ-5D-5L
- Cough visual analogue scale (VAS)
- Living with Pulmonary Fibrosis (L-PF) questionnaire
- Health/social care Resource Use Questionnaire
- Patient Global Impression of Severity (PGI-S) Scale

***Where possible, all questionnaires should be completed electronically during the clinic visit; if any technical issues occur, or if the participant requests it, paper copies of the

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questionnaire can be used. If the participant is unable to complete the questionnaires during their clinic visit there will be an option for them to complete at home.

7.6. Randomisation

The randomisation sequence, using variable block sizes, will be generated by an unblinded statistician and implemented through the bespoke web-based randomisation service provided by the Centre for Healthcare Randomised Trials (CHaRT), ensuring allocation concealment and replicability. Blinded kit lists will be generated by an unblinded statistician and provided to CHaRT before the trial is open to recruitment.

Randomisation of a participant can take place after informed consent, once all the pre-screening and baseline assessments have been completed and the participant's final eligibility has been confirmed. Eligibility must be assessed and confirmed by the PI or an appropriately qualified and delegated medically qualified doctor before a participant is randomised. Participants will then be randomised, using block randomisation, on a 1:1 basis to either prednisolone or placebo. Randomisation can occur the same day as the baseline assessments are completed if all information is available to make a final assessment of eligibility, or at most within a 7-day period from the date of the baseline assessment visit.

Participants will be randomised into the trial by a delegated member of the site team using an online randomisation service.

ONLINE ACCESS FOR 24-HOUR RANDOMISATION

Further information on how to randomise can be found in the separate 'Randomisation' work instruction contained in the Investigator Site File.

In any case where technical issues prevent the site team from accessing the online randomisation service, ExeCTU staff will be available within office hours to randomise on behalf of a delegated member of the site team. **Please note no ExeCTU back-up will be available out of office hours or on University of Exeter closure days (sites will be notified of these dates ahead of time).**

Once the online randomisation process is complete, the system will indicate to the user the blinded IMP kit IDs which should be dispensed to the participant. It will not indicate whether the participant has been allocated to receive IMP or placebo, as the allocation will be blinded to participants, research teams and pharmacists at sites and the trial team at ExeCTU (with the exception of the unblinded statisticians and authorised members of the ExeCTU trials team who will have no role in the day-to-day management of the trial).

The online randomisation system will automatically send an email to ExeCTU and the site research team, including the PI and pharmacy staff, confirming the randomisation has taken place and the kit IDs allocated. Site staff should note in the medical records that the patient has been enrolled into the trial. Site staff will then complete and send the approved letter to the participant's GP (e.g. via post or secure email) informing the GP that their patient has entered the trial.

7.7. Blinding

This trial will be double-blinded and therefore neither research teams at sites nor participants will know which treatment has been allocated. This will be achieved by the IMP manufacturer over-encapsulating, packaging, and labelling the IMP and placebo doses to look identical. The IMP/placebo packs will be labelled with blinded kit IDs and the randomisation system will automatically assign a kit ID to be dispensed to the participant after randomisation is complete. Only the unblinded statisticians, the IMP manufacturer and the developers of the

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randomisation system will have access to the master list which will indicate which pack IDs relate to placebo packs and which relate to prednisolone packs.

With the exception of the unblinded statistician(s) and authorised members of the ExeCTU trials team who will have no role in the day-to-day management of the trial. Where possible, all other members ExeCTU trials team will remain blinded.

7.7.1. Emergency unblinding

A trial-specific procedure is in place for emergency unblinding; this will be available 24/7 via a dedicated and automated phoneline. Further details will be provided in a separate unblinding work instruction.

If the person requiring the unblinding is a member of the investigating team, then a formal request to the PI or other delegated member of the team will be made who will then call the phoneline to trigger the unblinding.

Although the safety of the trial participants must always take priority, maintenance of the blinding is crucial to the integrity of the trial. Unblinding is strongly discouraged and should only occur for medical or safety reasons. Investigators should only break the blind when information about the participant's trial treatment is clearly necessary and will alter the appropriate medical management of the participant.

An assessment to unblind should be made in consultation with the clinical and research teams wherever possible. The treating clinician has the ultimate decision and right to unblind the participant.

ACCESS FOR 24-HOUR UNBLINDING

Further information on how to unblind can be found in a separate 'Unblinding' work instruction in the Investigator Site File.

Each time an unblinding occurs, an email alert will be sent to ExeCTU and the site team, informing them that the unblinding has happened (this email will not reveal the allocation). A member of the site team should document the details of the unblinding and reasons for it on the 'Unblinding' eCRF and in the medical notes.
Following an emergency unblinding the participant should be treated according to the treating clinician's assessment.

Trial oversight committees, where required within their charters, will also be notified of any unblinding.

7.8. Follow-up assessments

7.8.1. Telephone follow up visits

All participants will be contacted via telephone* at week 4 and week 8 post-randomisation; this is a safety precaution during the IMP dose reduction phase of the treatment schedule. During these calls, delegated research team should ask the participant if they have experienced any adverse events, if there have been any changes to their concomitant medications and the participant's self-reported IMP compliance (please see trial assessments in section 7 and assessment of compliance in section 8.11).

**Please note if there any safety concerns the participant can be seen in clinic for these visits.*

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7.8.2. In person follow up visit

All participants will be asked to attend an in-person visit at week 12 post-randomisation (-14 days /+7 days) with a delegated member of the site research team. During this visit participants will return their unused IMP dispensed at the baseline visit and will be prescribed and dispensed a new supply of IMP (see section 8.6.1).

Data to be collected during this visit will include:

- Pulmonary function measurements
    - Spirometry: forced vital capacity (FVC)
- Participant's self-reported IMP compliance and dose modifications review
- IMP prescribed and dispensed
- Unused IMP collected from participant and returned to pharmacy for the purpose of safe disposal
- Adverse event review
- Concomitant medication review
- Additional immunosuppressant or antifibrotic medication review

*Questionnaires (participant completed)**

- EQ-5D-5L
- Cough visual analogue scale (VAS)
- Living with Pulmonary Fibrosis (L-PF) questionnaire
- Health/social care Resource Use Questionnaire
- Patient Global Impression of Severity (PGI-S) Scale

* Where possible, all questionnaires should be completed electronically during the clinic visit; if any technical issues occur, or if the participant requests it, paper copies of the questionnaire can be used. If the participant is unable to complete the questionnaires during their clinic visit there will be an option for them to complete at home.

7.8.3. End of treatment in person follow up visit

All participants will be asked to attend an in-person end of treatment visit at week 26 post-randomisation (-14 days /+ 7 days) with a delegated member of the site research team. During this visit the participant will be prescribed and dispensed IMP prednisolone/ placebo 1mg to complete the weaning phase (see section 8.6.2).

Data to be collected during this visit will include:

- Pulmonary function measurements
    - Spirometry: forced vital capacity (FVC)
    - Gas transfer: DLco/TLco
- IMP prescribed and dispensed
- Participant's self-reported IMP compliance and dose modifications review

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- Check with participant has sufficient prednisolone/ placebo 5mg capsules to start weaning period (they will continue their 5mg supply dispensed at week 12 follow up visit)
- Waist circumference and weight
- Adverse event review
- Concomitant medication review
- Additional immunosuppressant or antifibrotic medication review

*Questionnaires (participant completed)**

- EQ-5D-5L
- Cough visual analogue scale (VAS)
- Living with Pulmonary Fibrosis (L-PF) questionnaire
- Health/social care Resource Use Questionnaire
- Patient Global Impression of Severity (PGI-S) Scale

*Where possible, all questionnaires should be completed electronically during the clinic visit; if any technical issues occur, or if the participant requests it, paper copies of the questionnaire can be used. If the participant is unable to complete the questionnaires during their clinic visit there will be an option for them to complete at home.

7.8.4. End of study telephone follow up visit

All participants will be contacted via telephone* at week 35 post-randomisation. During this call, a delegated research team member should ask the participant if they have experienced any adverse events, if there have been any changes to the concomitant medications or if they have been prescribed any additional immunosuppressant or antifibrotic medication. The participant will be asked to self-reported IMP compliance during the weaning phase (see section 8.6.2) The participant can return any unused medication to pharmacy at their next standard of care clinic visit for the purpose of safe destruction as per the hospitals local policy.

7.9. Withdrawal and change in participation status

Participants are free to discontinue from some or all aspects of the trial at any time if they wish to do so, without having to give a reason and without detriment to their ongoing care. In addition, a participant may be withdrawn from any aspect of the trial at the request of a healthcare professional if they feel it is within the best interest of the participant. In accordance with regulatory guidance, trial data that have already been collected will continue to be retained and used in the analysis.

Participants will be able to flexibly change their participation in the trial by selectively withdrawing from one, some or all of the following aspects:

- Discontinuation of allocated trial treatment but continue to attend trial follow up visits
- Discontinue allocated trial treatment and withdrawal from trial follow up visits but allow for passive data collection from medical records

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- Withdrawal from the trial completely and explicitly request no further data is collected from their medical records (except where required for reporting of serious adverse events)
- Optional collection of CT scan performed as standard of care and stored with a third party vendor
- Optional collection of a one-off blood samples at baseline and 12 weeks to be shipped and stored to a central laboratory for future genotyping and other mechanistic work
- If they would like to receive trial newsletters
- If they would like to receive the trial results and their allocation at the end of the trial

Participants who withdraw consent for trial participation prior to randomisation will be withdrawn from the trial completely and no further data will be collected. These participants will not count towards the recruitment target.

PeRSEVERE principles will be followed for participants who cease to engage with the trial (see: https://perseverepriciples.org/). If a participant becomes uncontactable and stops engaging with the trial, passive data collection will continue where available from the medical notes unless the participant expressly indicates they wish to fully withdraw from this.

If a participant is not engaging with the trial at a particular follow-up visit, reasonable attempts will still be made to contact them at the next timepoint unless they expressly indicate they wish to withdraw (e.g. if they don't answer their phone at the week 4 timepoint, attempts should still be made to complete the week 8 follow-up call).

If it becomes apparent that a participant has lost mental capacity and is unable to complete a follow-up timepoint, this will be recorded in the eCRF. Participants who lose mental capacity during the trial will be withdrawn in full and their original consent will no longer apply. Data and samples collected up to the point of withdrawal will be retained but no further data or samples will be collected.

All participants who change their participation status, or cease engaging with the trial, will still have the option to receive information about the trial, including newsletters and end of trial results unless they opt not to receive them.

The details and reason for change in participation status will be recorded in the participant's 'Change in Participation' eCRF and medical notes.

7.9.1. Discontinuation of trial treatment

If a randomised participant decides that they no longer wish to continue receiving trial treatment they should continue their trial follow up visits in accordance with the protocol unless they also request to be withdrawn from this aspect of the trial.

If the participant commenced their allocated trial drug and subsequently chooses to withdraw from trial treatment (or is withdrawn due to loss of mental capacity), it is recommended that the participant completes the weaning period off their medication (see dose schedules in section 8.6). Depending on the dose the participant is receiving at the time of the discontinuation, they may require a slower weaning period; this is at the discretion of the PI or delegated medically trained doctor.

If a participant chooses to withdraw from both trial treatment and follow up visits, passive data collection of safety data and additional therapies for FHP from medical records will be collected where possible unless the participant explicitly requests their medical records are not accessed.

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The participant should not be unblinded unless it is considered medically necessary for the participant's safety by a medically qualified doctor.

7.10. Collection and storage of CT scans and blood samples

As part of the trial, participants can provide optional consent for collection of blood samples and for copies of their CT performed as standard of care to be used for future research.

7.10.1. Collection, transfer and storage of CT scans

Participants are not required to have any additional CT specifically for the trial; however, participants will be asked if their CT scan(s) performed as standard of care can be collected and stored for future research. This will include the CT scan reviewed at their MDT to confirm a diagnosis of FHP, and any additional CT scan(s) performed during the participants' routine follow up for FHP during their participation in the trial.

If a participant agrees to this optional component of the trial (as indicated on the informed consent form), the CT scan(s) will be pseudonymised by the local site with participant ID number and sent to a third-party vendor (Qureight Ltd). Qureight Ltd are a UK based company that routinely receive and store NHS patient CT scans through their secure online portal. CT scans from consenting participants will be uploaded by the local site to the Qureight portal. Details of how to complete this process will be provided in a 'Submitting CT scans for future research' work instruction. The CT scans will be stored securely by Qureight in compliance with UK GDPR. Qureight is registered with the NHS Data Security and Protection toolkit.

7.10.2. Blood samples for future research

If a participant provides consent to collect bloods samples for future research, these will be collected at the baseline visit and the week 12 follow up visit. The whole blood will be obtained and shipped ambient via post (in a Royal Mail Safe Box) to the Exeter NIHR Clinical Research Facility at Royal Devon University Healthcare NHS Foundation Trust (a Human Tissue Authority licenced laboratory). Details of this process will be provided in a 'Blood for future research' work instruction. Once the samples have been received at the Exeter Clinical Research Facility, they will be processed and stored at -80°C as serum, plasma and whole blood. Any remaining blood samples that were stored for future research will be destroyed after 15 years.

7.11. End of trial

The end of the trial is defined as when the last participant has completed their week 35 end of study telephone follow up, all data queries have been resolved, the trial database has been locked and pre-specified analyses are complete. A declaration of end of trial form will be submitted to the MHRA and NHS REC that awarded the favourable opinion within 90 days of the end of trial.

If the trial is terminated early, the trial will end on the date the Sponsor formally declares the trial terminated in writing. The MHRA and NHS REC will be notified of early termination within 15 days of the Sponsor deciding to end the trial.

8. TRIAL TREATMENTS

Participants will be randomised to receive either 26 weeks prednisolone or 26 weeks placebo on a 1:1 ratio.

8.1. Name and description of investigational medicinal product(s)

Prednisolone is the IMP in this trial with a matched placebo. Prednisolone is the standard corticosteroid used for lung conditions in the UK (except for COVID-19 pneumonia). In the

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CHORUS trial, the tablet oral form of prednisolone is being used in both 5mg and 1mg doses, which are over-encapsuled. There will be a matched placebo oral capsule.

8.2. Regulatory status of the drug

Prednisolone has marketing authorisation in the United Kingdom.

The IMP is being processed for this trial (for blinding purposes) in the following ways: deblistering and over-encapsulation with backfill, before repackaging into secure tamperproof containers, with blinded labels as per MHRA annex 13 labelling requirements. IPS Pharma will be contracted to complete these activities. The capsules are HPMC green/green size 00 capsules containing Hydroxypropylmethylcellulose, water, Dye – copper complex of chlorophyllins E141ii. The placebo capsule will be backfilled with an excipient of prednisolone. Full details can be found in the Investigational Medicinal Product Dossier (IMPD).

8.3. Product Characteristics

For details of product characteristics, please refer to the provided Summary of Product Characteristics (SmPC).

8.4. Drug storage and supply

Full details can be found in the pharmacy manual. The prednisolone and placebo will be provided directly to sites by the contracted IMP supplier. It will be delivered to sites in batches with the first delivery prior to site greenlighting to open to recruitment. Deliveries will be receipted by the pharmacy department at sites and recorded as received on a trial specific IMP management database. If stock of the trial drug (and placebo) packs is required to be stored away from the local site pharmacy for any reason, please contact ExeCTU for approval.

A drug accountability record will be maintained and updated by delegated site staff for all IMP packs provided and dispensed. The delegated persons at the sites will keep records of the receipt, dispensing, returns, quarantine or destruction of trial medication. The blinded pack IDs will be used to identify the packs on the accountability logs. A file note should be included in the Pharmacy Site File (PSF) directing to the location of these records. At the end of the trial, the drug accountability record should not be destroyed without Sponsor authorisation. All data regarding the trial medication must be recorded either on forms provided by ExeCTU or on local accountability forms authorised by ExeCTU.

8.5. Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of the IMP will be completed by the contracted IMP supplier IPS pharma in accordance with annex 13 of Good Manufacturing Practice (GMP) guidelines. Full details can be found in the pharmacy manual.

For blinding purposes, the active drug will be over-encapsulated. Placebo capsules will be manufactured to match in appearance but will not contain any active ingredients.

Active and placebo capsules will be packaged both strengths will be packed into High Density Polyethylene (HPDE) containers with a poly propylene child resistant cap (120 capsules per container for the 5mg dose and 100 capsules per container for the 1mg dose) with tamper-evident seals. All containers will be labelled with unique pack IDs.

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8.6. Dosage schedules

The IMP packs to be prescribed and dispensed to the participant upon randomisation will be allocated by the randomisation system within the main trial database (REDCap) by the research team.

For subsequent dispensing visits, and the allocation of single additional packs, site research staff must log directly into the IMP management system (IMP-MS) to allocate the packs. For further details please see pharmacy manual.

The Randomisation system or IMP-MS will automatically return the correct quantity of pack IDs of the correct type and dose (1mg or 5mg prednisolone or 1mg or 5mg placebo) for the specific visit. Confirmation of the pack IDs will be emailed to the site team (PI, research nurses/coordinators and pharmacy team).

At their baseline visits participant will be provided with a trial treatment diary with guidance of how to take their trial treatment and their planned daily dose schedule.

8.6.1. Intervention period

Prednisolone 5mg or matched placebo

For the intervention period (weeks 0 to 25) participants will be provided with over-encapsuled prednisolone/ matched placebo in 5mg (or equivalent) capsules. Prednisolone 5mg or matched placebo will be prescribed and dispensed at baseline (at randomisation) and the in-person week 12 follow up visit.

An initial peak dose of 40mg (8 capsules) per day will be given for two weeks, followed by dose reduction of 10mg until reaching a maintenance dose of 10mg (2 capsules) per day by week 12 post-randomisation (i.e. 40mg/day (8 capsules) for 2 weeks, then 30mg/day (6 capsules) for 4 weeks, then 20mg/day (4 capsules) for 4 weeks, then 10mg/day (2 capsules) maintenance). The maintenance dose of 10mg/day (2 capsules) will be continued for the remainder of trial intervention period (i.e. to 26 weeks post-randomisation). See Table 3 and Figure 3 for details.

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Table 3: Trial treatment schedule

Treatment Day	Total daily dose (if on active treatment)	Prednisolone 5mg/placebo Capsule(s)/day	Prednisolone 1mg/placebo Capsule(s)/day	Number of weeks taken
Dispensing visit- Baseline				
0-13	40mg	8	0	2
14-41	30mg	6	0	4
42-69	20mg	4	0	4
70-83	10mg	2	0	2
Dispensing visit- Week 12				
84-181	10mg	2	0	14
Dispensing visit- Week 26				
182-188	5mg	1	0	1
189-202	4mg	0	4	2
203-216	3mg	0	3	2
217-230	2mg	0	2	2
231-245	1mg	0	1	2
Week 35 End of study				

All participants will be provided with additional prednisolone 5mg/matched placebo to act as a "buffer" for trial compliance, medically approved dose escalations and late follow-up visits. See Dose modification section 8.7

8.6.2. Weaning period

Prednisolone 1mg or matched placebo

For the weaning period (week 26 to 34) participants will be provided with over-encapsuled prednisolone/ matched placebo in 1mg (or equivalent) capsules. The weaning schedule is summarised in Table 3 and Figure 3. Prednisolone 1mg or matched placebo will be prescribed and dispensed at the end of treatment week 26 in person visit.

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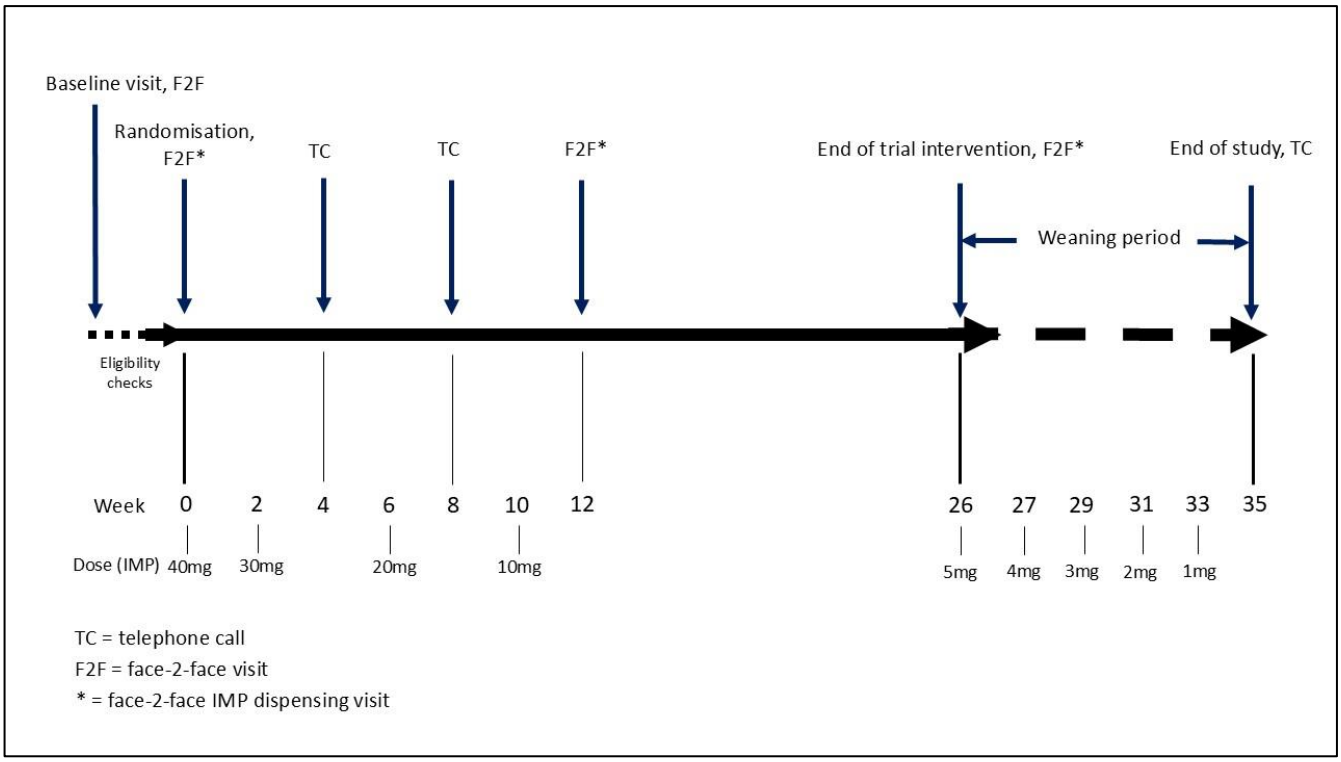

Figure 3: Dose schedule, visits and weaning period

The planned dose schedule for the intervention and weaning periods along with the scheduled participant contact visits are documented in Figure 3. The weaning period (week 26 to 34) was designed to mitigate against the risk of possible adrenal suppression. The weaning algorithm shown in Figure 4 was produced in collaboration with endocrinology colleagues Professor Andrew Hattersley, Dr Antonia Brooke, Dr Julia Prague from Royal Devon University Healthcare Foundation Trust.

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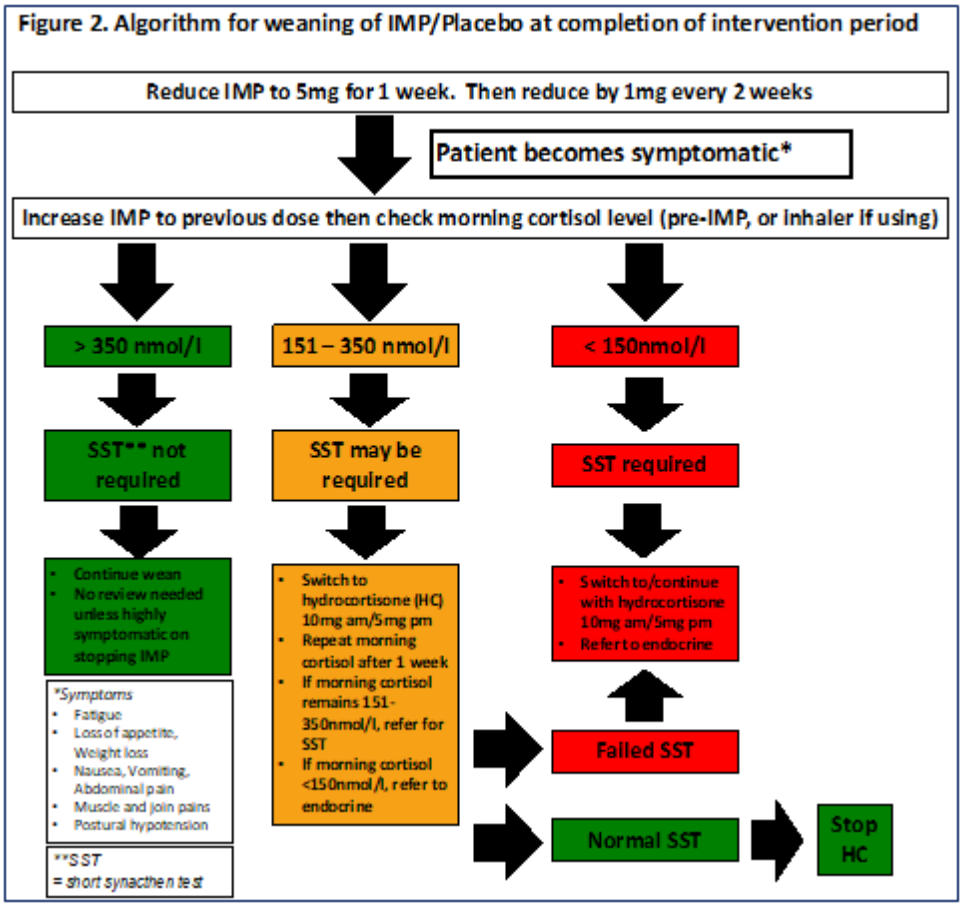

Figure 4: IMP weaning algorithm

8.7. Dosage modifications

This trial has been designed to mimic clinical practice wherever possible and it is anticipated that investigators may want to increase the IMP for short periods of time based on clinical events, such as 1. Intercurrent infections/exacerbations or 2. perceived respiratory deteriorations (symptomatically) on dose titration from 40mg to 10mg. Or investigators may want to dose reduce from 40mg to 10mg at faster rate than outlined in section 8.6.1 for example if the participant experiences significant psychiatric events believed to be related to higher doses of prednisolone.

Participants have been provided with additional IMP to allow a short-term increase in IMP to occur in a blinded fashion. While the final decision on dosage will be left to discretion of the treating local investigators, we would recommend the following:

1. For intercurrent infections/exacerbations: a standard escalation to 6 capsules (30mg) for 7 days, with reduction thereafter back to previous dose of IMP
2. For perceived deteriorations in symptoms during the titration period (Days 0 to 70) then the local investigator may increase the IMP to the last previously effective dose for 7 days, then reattempt a further wean down to the planned dosing schedule.

If the dose modifications are not successful then the local investigator should contact the trials team to discuss the appropriate next steps.

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8.8. Known drug reactions and interaction with other therapies

A full list of known adverse effects of prednisolone is detailed in the Summary of Product Characteristics (SmPC). Please see the risk section 2.1 for more information of the key safety risks.

8.9. Concomitant medication

All concomitant medications including over the counter medications should be reported on the concomitant medications eCRF in REDCap.

8.9.1. Non-permitted concomitant medication

Participants are not permitted to take any the following medication whilst in the CHORUS trial:

- **Hepatic microsomal enzyme inducers/ Antiepileptics:** phenytoin, rifabutin, carbamazepine
- **Hepatic microsomal enzyme inhibitors/ antifungals**: ketoconazole
- **Antibacterials:** Rifamycin

If a participant has taken or is currently any of the non-permitted concomitant medications, please contact the CHORUS trial manager via CHORUS@exeter.ac.uk for further advice.

A full list of prednisolone interactions can be found in the prednisolone SmPC.

8.9.2. Additional immunosuppressive therapies

After the week 12 follow up visit, additional immunosuppressive therapies can be prescribed at the discretion of the investigating site, which can include second line mycophenolate and azathioprine and the addition of anti-fibrotics, nintedanib. Any additional immunosuppressive therapies should be reported on the additional therapies eCRF in REDCap.

8.9.3. Supportive medication

Investigating sites should assume that the participants are on prednisolone and can prescribe any supportive medication supplied as usual standard of care. Any supported medications should be reported on the concomitant medications eCRF in REDCap.

8.10. Trial restrictions

Participants of childbearing potential are required to use highly effective contraception for the duration of their participation in the trial (35 weeks from randomisation), as defined in the eligibility criteria section 6. Breastfeeding mothers and pregnant people are not eligible to participate in this trial.

8.11. Assessment of compliance with treatment

Every randomised participant will be provided with a participant trial treatment diary. This will be used to help the participant to log their daily trial treatment and record any side effects they may have experienced.

This participant trial treatment diary can be used by the participant during their follow up visits to inform the research team of any adverse events, missed doses or dose modifications that have occurred since the last visit, or to confirm the trial treatment has been taken as planned. Please note these diaries can be reviewed by the research team however they will not need to be transcribed in REDCap.

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During their follow up visits participants will be ask to self-report their IMP compliance by answering the following question;

Since your last follow-up visit, which of the following options best describes

how often you took your trial treatment?

- Never
- Less than half the time
- About half the time
- More than half the time
- Nearly all the time
- All the time

This will be recorded on the visit follow up eCRFs. If the participant has been advised by their clinical team at the hospital to modify their trial treatment dose (see section 8.7) this should be recorded on the IMP Dose modification eCRF in REDCap. For guidance on how to report adverse events or serious adverse events reported at the follow up visits please see pharmacovigilance section 9.

Participant will be advised to return all unused IMP during their follow up visits for safe disposal, all IMP can then be destroyed in accordance with local pharmacy practice.

The local trial pharmacy teams will be responsible for maintaining and updating the drug accountability log in the CHORUS Pharmacy Site File (PSF) or ISF as per the CHORUS pharmacy manual.

9. PHARMACOVIGILANCE

9.1. Definitions

Table 4: Adverse event definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and

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	the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect **In addition for this trial** • **acute respiratory exacerbations that require attendance to accident and emergency (A&E) will be reported as an SAE** Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

Severity classifications

Table 5: Adverse event severity classifications

Mild event	An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
Moderate event	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe event	An event that prevents normal everyday activities.

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9.2. Expected adverse events associated with a trial drug

The reference safety information (RSI) for this trial is section 4.8 of the supplied pharmacovigilance reference copy of the prednisolone SmPC.

9.3. Recording and reporting of Adverse events (AEs)

The safety reporting period will begin from the time of randomisation up to the week 35, End of Study telephone follow-up. The recording and reporting requirements are summarised in the safety reporting flowchart in Figure 5. Adverse events should be reviewed at every follow up visit.

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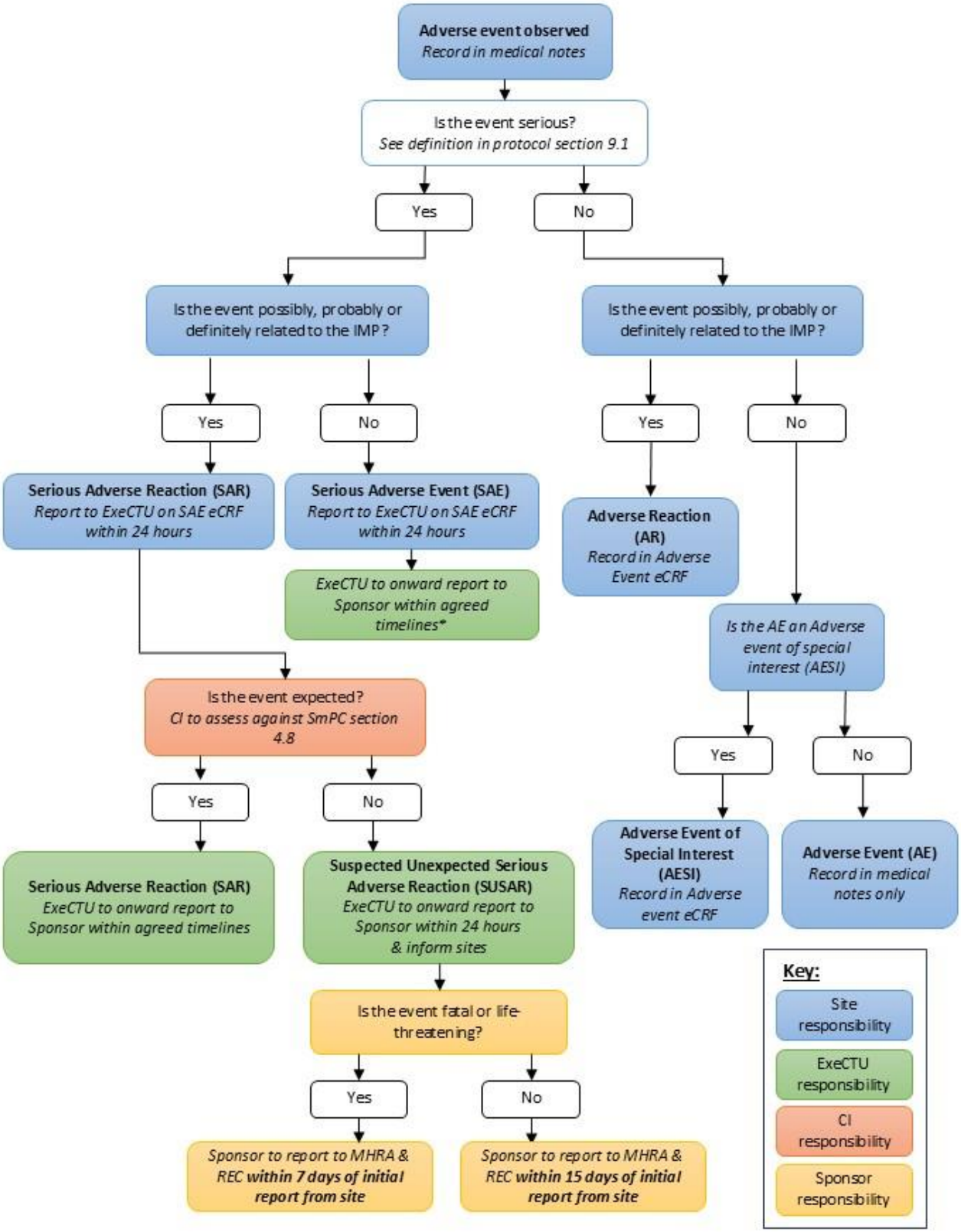

Figure 5: Safety reporting flow chart

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All adverse events will be assessed for seriousness and causality as per the definitions in section 9.1 above. These assessments should be carried out by the site PI, or delegated medically qualified doctor, and recorded in the medical notes. If the adverse event is possibly, probably or definitely related to prednisolone it is considered an adverse reaction (AR) and must be reported in the adverse event eCRF in REDCap. In addition to this any viral, fungal or bacterial infections of any kind are considered Adverse Events of Special Interest (AESI) for this trial and must be reported on the adverse event eCRF. If the adverse event doesn't meet the definition of serious and is not considered to be an AESI or AR it should only be documented in the participants medical notes but not be reported on the adverse event eCRF.

All related and unrelated adverse events that are considered serious, as defined in section 9.1, must be reported as an SAE. Additional guidance for reporting serious adverse events can be found in section 9.4 below.

As this is a blinded trial, adverse events should be evaluated on the assumption that the participant was allocated the active drug i.e. prednisolone. The blind should only be broken where knowing the allocation is clearly necessary and will alter the appropriate medical management of the participant. If unblinding is necessary, please refer to the Emergency Unblinding section of the protocol (7.7.1) and the CHORUS 'Unblinding' working instruction.

9.4. Recording and reporting Serious adverse events (SAEs, SARs, SUSARs)

All related and unrelated adverse events that meet the protocol definition of serious must be reported to ExeCTU within 24 hours of the PI, delegate or research team becoming aware by completing the 'SAE' eCRF in REDCap.

All SAE eCRFs must be reviewed and signed off by a PI or delegated medically qualified doctor, within REDCap. In the event of a death, the Death eCRF should be completed ***in addition*** to the SAE eCRF in REDCap. Any information not available at the time of the initial report (e.g. test results) must be added to the SAE eCRF by the site team as soon as it becomes available.

For each SAE the following information will be collected:

- Full details in medical terms with a diagnosis (if available)
- Event duration (date of onset and date of resolution)
- Reason for seriousness
- Trial drug details
- Action taken
- SAE outcome
- Causality and severity, in the opinion of PI (or medical delegate)

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ExeCTU will receive an automated email notification to alert them to a new SAE eCRF or when a change is made to an existing SAE eCRF. In the event of a SUSAR the site will be contacted by the CHORUS trial manager and it may be requested that further details are added SAE eCRF please refer to safety work instruction.

9.4.1. Reviewing serious adverse events

The CI or designated representative will review all reported SAEs to assess causality. Where in either the opinion of the PI and/or CI the SAE is considered possibly, probably or definitely related to the IMP, an assess expectedness to the IMP will be made prednisolone SmPC which serves as the Reference Safety Information (RSI) for the trial. The CI will not downgrade a PI's assessment of causality; however, they may upgrade a PI's assessment of causality (i.e. from unrelated to related).

Sites should respond as soon as possible to requests for further information by the CI or designated representative required for the final assessment of the SAE.

In the event of a SUSAR, ExeCTU will take responsibility for unblinding prior to submission of the SUSAR to the MHRA and the REC. Local investigators will only receive information on the results of the unblinding if it is judged necessary for the safety of the participant. ExeCTU will onward report SUSARs to the Sponsor within 24 hours of becoming aware but all other SAEs reported will be reviewed by the sponsor in bulk (e.g. as listed in TMG reports).

The DMC will periodically review unblinded safety data for each treatment group separately to determine patterns and trends of events, or to identify safety issues that would not be apparent on an individual case basis.

The TSC will periodically review blinded, pooled safety data and liaise with the DMC regarding safety issues.

9.4.2. Ongoing events

Some SAEs/SARs/SUSARs may be ongoing at the time of initial reporting.

It is the PI's (or medical delegate's) responsibility that all SAEs/SARs/SUSARs are followed up until the final outcome is reached or up to the end of the study visit at week 35 post-randomisation. There is no mandatory requirement regarding the frequency which follow-up reports should be submitted; however, follow-up information should be entered into the eCRF as soon as the PI (or medical delegate) becomes aware of the outcome.

Ongoing SAEs/SARs/SUSARs at the end of the trial will be followed up by the participant's GP and/or the routine clinical care team until discharge.

9.4.3. Notification of deaths

Irrespective of whether the death is related to the intervention or if it is unrelated, all deaths occurring during the safety reporting period must be reported to ExeCTU and the Sponsor within 24 hours of the PI or research team becoming aware of the event. This will be reported by completing an 'SAE' eCRF and 'Death' eCRF in REDCap.

9.4.4. Expedited reporting of SUSARs

If a SUSAR is reported by a site, the Sponsor will coordinate onward reporting to the REC and the MHRA (required within 7 calendar days of receipt of the initial report for fatal/life-threatening events or 15 calendar days of receipt of the initial report for non-fatal/non-life-threatening events)

All other recruiting sites will be informed of the SUSAR by ExeCTU.

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9.5. Responsibilities

The CI is responsible for oversight of the safety of participants in the trial, including an ongoing review of the risk/benefit. They will review SAEs causality using their medical judgement and review all SARs for expectedness using the RSI in a timely manner.

The CI (or delegate) will review and confirm the Medical Dictionary for Regulatory Activities (MedDRA) coding assigned by the team at ExeCTU to all reportable safety events.

9.6. Pregnancy reporting

In the event of a pregnancy being reported by a female participant, this must be reported using an ExeCTU 'Pregnancy' eCRF within 24 hours of learning of its occurrence. All pregnancies from randomisation until Week 35 End of Study telephone follow up should be reported. Please note, the completion of the pregnancy eCRF is only required to if a trial participant is pregnant; notification is not required if a participant's partner becomes pregnant.

If a pregnancy is reported during the intervention period, the pregnant participant should be unblinded (see blinding section 7.7) and their clinical management directed by the local PI. Pregnant participants should continue to complete trial follow-up visits unless they withdraw consent. No additional trial follow-up is required for participants who become pregnant during the trial. Due to the minor teratogenic risk of prednisolone, pregnancy outcomes will not be collected for this trial. The British National Formulary states that the benefit of treatment with corticosteroids during pregnancy outweighs the risk (https://bnf.nice.org.uk/drugs/prednisolone).

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the protocol definition of serious, a serious adverse event eCRF must be completed (see pharmacovigilance section 9).

9.7. Overdose

As per the SmPC for prednisolone, reports of acute toxicity and/or deaths following overdose with glucocorticoids are rare and no specific antidote is available. Treatment should be supportive and guided by symptoms.

All participants that have taken an overdose of IMP should be treated as though they are on the active treatment. Participants should be monitored as per local standard of care practice.

The risk of overdose in the trial has been assessed by the CI as part of the detailed risk assessment.

Any overdose resulting in attendance to A&E or considered significant as assessed by treating clinician must be reported on the 'Non-Compliance' form). If an overdose results in adverse events that meet the protocol definition of serious, a serious adverse event eCRF must be completed in REDCap ***in addition*** to the 'Non-Compliance' form (see pharmacovigilance section 9).

9.8. Reporting urgent safety measures

The Sponsor, CI, co-lead, PI, DMC and/or TSC may take appropriate urgent safety measures (USM) in order to protect the participants of a clinical trial against any immediate hazard to their health or safety.

If a PI implements a USM at a site, they must inform the CI immediately (see contact details in key trial contacts section and copy ExeCTU; CHORUS@exeter.ac.uk). If time permits, the investigator should discuss any proposed actions with the CI prior to implementation. A record of all discussions, decisions, and actions taken must be recorded in the Investigator Site File.

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The CI or delegate will inform the Sponsor within 24 hours to discuss the hazard and any actions taken (prior to implementation if time allows). USMs identified shall take immediate effect and the CI or Sponsor will telephone the REC and MHRA ideally within 24 hours (no later than 3 days) to discuss the event with a medical assessor. The CI, Sponsor (or delegate) will further notify the REC and MHRA in writing within 3 days from the date the measures were taken.

If the CI and the Sponsor consider the USM to affect all participants, ExeCTU will inform all PIs of the USM under the CIs oversight.

9.9. The type and duration of the follow-up of participants after adverse reactions.

All SAEs/SARs/SUSARs are followed up until the final outcome is reached or up to the end of the study visit at week 35. Participants should be monitored as per local standard of care practice and treatment should be supportive and guided by symptoms.

9.10. Development safety update reports

A DSUR will be provided to the MHRA and REC by ExeCTU at the end of each reporting year. The CI (or designated representative) in collaboration with ExeCTU will prepare all relevant information for the DSUR. The Sponsor will review the DSUR prior to submission and the CI will review the clinical sections and provide final sign off prior to submission.

10. STATISTICS AND DATA ANALYSIS

10.1. Target sample size

The target is 222 randomised participants. The sample size calculation is based on a group sequential design with one interim analysis (i.e. total of two looks including the final analysis), using the O'Brien-Fleming spending function. The trial is powered at 90% to detect a between-group difference in change in absolute FVC between baseline and 26 weeks post-randomisation of 58ml, at the 5% two-sided significance level, conservatively assuming a standard deviation (SD) of change in absolute FVC between baseline and 26 weeks post-randomisation of 125ml and allowing for 10% loss-to-follow-up. The target difference is therefore equivalent to a standardised effect size of 0.464. This target difference was informed from data from the INBUILD trial as well as other published trials of fibrosing lung disease (CAPACITY, INPULSIS and ASCEND) [27-30]. The target difference was discussed and agreed with clinicians taking part in the trial and patient representatives. See Appendix 1 for power scenarios based on the planned recruitment target.

There is a planned review (at the time of the interim analysis) of the pooled standard deviation of change in absolute FVC between baseline and week 26, with a blinded sample size re-estimation undertaken if indicated. If the observed pooled SD is larger than expected, implications on the required sample size will be discussed, taking into account other factors such as the emerging retention rate at the primary endpoint and rates of completeness of the primary outcome, and remedial action will be considered if deemed necessary.

10.2. Planned recruitment rate

The target is 222 participants randomised over a 25-month recruitment period. The projected mean randomised rate/site/month is ~0.4 participants. The projected recruitment period (25 months) allows for staggered opening of the estimated 30 sites required, with the initial focus on opening 10-15 sites during the first 12 months of the recruitment period as part of the internal pilot phase. The recruitment/randomisation rate will be regularly reviewed by the TMG and trial oversight committees; additional sites may be sought if the recruitment rate is lower than predicted.

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10.3. Statistical considerations and statistical analysis plan

A detailed statistical analysis plan (SAP) [31] will be drafted by the trial statisticians, which will be reviewed and approved by an independent statistician prior to database lock. The planned statistical analyses will consider the ICH E9 guideline together with the more recent ICH E9 (R1) addendum on estimands [32]. The primary analyses will be conducted following the collection of the final follow-up data for the last participant, final data cleaning and database lock and data export to the trial statisticians.

Primary analyses of the primary and secondary outcomes will follow the treatment policy approach. Throughout the analysis, emphasis will be placed on estimation and between-group comparisons will be presented with two-sided 95% confidence/credible intervals, for both primary and secondary outcomes. Where hypothesis tests are carried out, the statistical significance level will be two-sided at the 5% level. Primary analyses for the primary and secondary outcomes will be adjusted for baseline measures relevant to the outcome under consideration. For completeness, simple unadjusted analyses will also be presented. No adjustments for multiple analyses will be made as the trial has a clearly specified primary outcome. Model assumptions will be visually checked, and bootstrapping implemented as required e.g. to handle substantial deviations from normality. The trial will be reported following the relevant Consolidated Standards Of Reporting Trials (CONSORT) guidelines [33, 34] and relevant extensions, including for Pragmatic Trials; Patient Reported Outcomes.

10.4. Participant analysis populations

The primary analysis population will include all participants as randomised (i.e. treatment policy strategy), who provide at least one post-baseline FVC measure: the primary analyses will include observed data in repeated measures models, allowing the inclusion of all participants who provide at least one post-baseline FVC measure. Primary analyses of secondary outcomes will similarly follow a treatment policy strategy.

Secondary analyses of the primary outcome will consider adherence with allocated treatment, i.e., based on participants who meet a minimum threshold of participant reported self-adherence with their allocated trial treatment; full details will be included in the SAP.

The secondary outcomes relating to safety (related adverse events, serious adverse events) will be considered on an as treated basis.

10.5. Summary of baseline data and flow of participants through the trial

Baseline characteristics of participants will be summarised descriptively by allocated group and used to assess for any marked baseline differences in demographics or outcome measures between the two allocated groups. Loss to follow-up after randomisation will be reported separately for each group, summarised visually via a CONSORT flow diagram. Baseline characteristics will be subjectively examined to assess for potential differences between participants who withdraw, discontinue treatment, and those who complete the trial.

10.6. Primary analysis of the primary outcome

The primary outcome in this trial is change in absolute FVC between baseline and 26 weeks post-randomisation. The primary analysis of the primary outcome will compare change in absolute FVC between allocated groups using a repeated measures (longitudinal) mixed-effects model to facilitate inclusion of participants who provide at least one post-baseline FVC (12 and/or 26 weeks), maximising use of available FVC data and minimising effects of loss-to-follow-up. This will model change in FVC at 12 weeks (i.e. baseline minus 12 weeks) and 26 weeks (i.e. baseline minus 26 weeks) via the inclusion of allocated treatment-by-time interaction terms, adjusting for pre-specified baseline variables (including baseline FVC) and site as a random effect.

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The estimated between-group difference in change in absolute FVC at 26 weeks will be extracted from this model, together with confidence interval, to obtain the primary result of the primary analysis.

It is noted that modelling absolute FVC at 26 weeks as the primary outcome, with adjustment for baseline absolute FVC, would give the same estimated treatment effect as modelling the change in FVC between baseline and 26 weeks (with adjustment in the model for baseline FVC). However, defining the primary outcome as change in absolute FVC was chosen on the basis of easier interpretation, as change in FVC is commonly used when discussing disease progression with patients and is also used in the majority of trials/research in this field.

Potential key intercurrent events (e.g. treatment discontinuation/withdrawal, death) will be considered, with the primary analysis using a treatment policy strategy i.e., all participants will be analysed according to the group they were allocated. This is line with the primary aim of the trial, which is to assess the effectiveness of prednisolone, in comparison with placebo, regardless of compliance with allocated treatment, therefore the primary analysis will be programmed and undertaken following the intention-to-treat principle.

10.7. Handling of intercurrent events in primary estimand

Intercurrent events related to adherence to treatment (i.e. discontinuation/withdrawal) will be handled using the treatment policy strategy; the treatment effect is estimated irrespective of the occurrence of such an intercurrent event. This policy is in alignment with an intention-to-treat analysis. Deaths during the trial will be handled using the “while alive” approach; participant data collected prior to death will be included in the analyses.

10.8. Sensitivity, subgroup and additional analyses of the primary outcome

Sensitivity, supporting and subgroup (e.g. subgroup of participants with clearly documented environmental exposure causing FHP) analyses of the primary outcome will be pre-specified in the detailed statistical analysis plan.

A linear mixed model will be used to combine all the post-randomisation absolute FVC results into a single model which will adjust for the same factors as the primary analysis of the primary outcome and include a participant identifier as a random effect. An interaction between allocated group and time will also be included to assess if any effect of prednisolone is constant over time or varies as time progresses.

The pattern of missing data will be assessed and if appropriate, a sensitivity analysis will use multiple imputation to account for missing primary outcome 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 worst-case scenario or pattern-mixture models.

With regards to capturing/assessing adherence, pill counts would not be viable due to participants being able to escalate the dose and risks of unblinding. Whilst participants will be asked to report their adherence to treatment, experience suggests that such data might not be complete or reliable. However, if sufficient numbers of participants self-report adherence/non-adherence, a complier average causal effect (CACE) analysis will be undertaken.

10.9. Adjusted analysis

Additional adjusted analysis may be undertaken including baseline factors found to be unbalanced between allocated at baseline and thought to be predictive of the primary outcome.

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10.10. Primary analysis of secondary outcomes

Secondary outcomes will be reported descriptively at each timepoint collected. Analysis of secondary outcomes, including the PROMS, will use similar mixed-effects models, with adjustments for baseline outcome where relevant, maximising the use of longitudinal data where possible. Binary outcomes (initiation of anti-fibrotic medication/additional immunosuppressive therapy; hospitalisations/acute exacerbations/death) will be analysed using logistic regression and time to event analyses, with adjustments in the models as per the primary analyses. Secondary outcomes assessing safety, such as related adverse events and serious adverse events, will be descriptively summarised only.

10.11. Procedure(s) to account for missing or spurious data

Reasons for being unable to collect data during an assessment will be recorded on the electronic case report form (eCRF), where appropriate. eCRFs will be assessed for missing data by ExeCTU and sites will be regularly chased for missing data. The ExeCTU will maintain a record of site compliance with eCRF completion. If data completion is poor, a triggered monitoring visit may be scheduled.

The eCRFs will include mandatory fields, which should be filled in before the eCRF can be saved to reduce the risk of missing data. Where questions may need to be left blank, options such as ‘Not applicable’ or ‘Prefer not to say’ will be available, to differentiate these from missing data. Validation rules will be set in to the REDCap database to check the entered data is in the expected data type and within an anticipated range. Manual queries will be raised on any data field where it is necessary to verify any discrepancies in the entered data, such as querying if the date of a visit does not correspond to the correct timepoint.

To reduce the risk of missing data for PROMs, participants will complete these during their (blinded) assessment visits, in between undergoing physical assessments. The local investigator will check for missing data as each PROM is completed.

10.12. Planned interim analysis and criteria for the premature termination of the trial

At the end of the first stage of this group sequential trial, a pre-specified interim analysis of the primary outcome (using O-Brien Fleming spending function for determination of boundaries) will be conducted to assess effectiveness and given sufficient evidence of activity of the drug, the trial will continue to the second stage. The single planned interim analysis will be undertaken after the first 100 randomised participants reach the primary endpoint (26 weeks post-randomisation). Full details of the interim analysis will be documented in the statistical analysis plan (or a separate interim analysis plan).

This interim analysis will also include a review of the pooled standard deviation of the change in absolute FVC between baseline and 26 weeks post-randomisation, with a blinded sample size re-estimation undertaken if indicated. If the observed pooled SD is larger than expected, implications on the required sample size will be discussed, taking into account other factors such as the emerging retention rate at the primary end point and rates of completeness of the primary outcome, and remedial action will be considered if deemed necessary.

This interim analysis is separate from the internal pilot phase (assessing trial progression over the first 12 months of participant recruitment (section 4.1)). The DMC will review the interim analyses and make a recommendation to the TSC regarding continuation of the trial.

10.13. Other statistical considerations

Any changes made to the SAP will be documented, including details of when the change was made (e.g. prior to data export).

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11. ECONOMIC EVALUATION

A full within-trial cost-effectiveness analysis (CEA) will be conducted to estimate the incremental cost-effectiveness of the prednisolone intervention as compared to placebo.

Resources and costs of providing prednisolone will be established. Participant health, social care and broader societal resource use will be captured at baseline, 12 week and 26 week follow-up using a self-report resource use questionnaire (RUQ). The RUQ will be tailored for this participant population, with input from trial PPI representatives and the trial co-applicants [35]. Nationally recognised UK health and social care unit costs will be applied to the resource use data [36]. QALYs will be estimated using EQ-5D-5L data collected at baseline, 12 week and 26 week follow-up visits. The 'cross-walk' algorithm [35] will be used to provide QALY weights from the EQ-5D-3L UK general population valuation survey, in accordance with the current 'position statement' of the National Institute of Health and Care Excellence (NICE) [37].

Descriptive statistics will summarise costs and QALYs by the prednisolone and placebo groups. Longitudinal mixed effects linear regression models will be undertaken to test for differences in costs and QALYs. Models will adjust for the same baseline factors controlled for in the primary trial analysis, with appropriate random and/or fixed effects. In addition, the cost regression model will adjust for baseline costs, and the QALY model for baseline EQ-5D-5L values. The CEA will synthesise cost and outcome data to present incremental cost-effectiveness ratios for: i) the trial primary outcome, in the form of cost per change in FVC at 26 week follow-up, and ii) the policy relevant economic endpoint, cost-per-QALY at 26 week follow-up. Sampling uncertainty will be accounted for in the analysis, and we will explore the pattern and potential mechanisms of missing data in considering multiple imputation. Cost-effectiveness acceptability curves will be presented as appropriate using the net-benefit approach. These will show the probability that the prednisolone intervention is cost-effective (as compared to placebo) over a range of cost-per-QALY thresholds (e.g. the £20,000 and £30,000 thresholds considered by NICE). The CEA will initially be undertaken from a primary perspective of the NHS and Personal Social Services, with broader societal perspectives considered in sensitivity analyses, informed by input from the PPI representatives. A Health Economics Data Analysis Plan (HEAP) will be developed, which will be fully concordant with the SAP and the internationally recognised CHEERs guidelines for reporting CEA studies [38, 39].

12. DATA MANAGEMENT

12.1. Data collection tools and source document identification

Local research teams will use the REDCap Clinical Data Management System (CDMS) provided by Exeter CTU to record participant data in accordance with the protocol. This CDMS will be the electronic CRF (eCRF). If direct data entry in REDCap is completed, this will be considered the source data, for example electronic PROMs and electronic consent forms. For data completed in participant medical records or on paper source data worksheets this will be considered the source data which is entered on the eCRFs in REDCap by the local research team.

The electronic randomisation and IMP management system is provided by Centre for Healthcare Randomised Trials (CHaRT; University of Aberdeen). The randomisation system will be integrated into CHORUS REDCap system and will not require a separate log in. IMP orders, receipt confirmation and individual pack statuses will be recorded directly in IMP-MS which is separate to the REDCap system and will require different login. IMP-MS must be kept up to date to ensure only available and non-expired drugs are able to be allocated by the system during randomisation. Sites will maintain local IMP accountability logs for the purposes of monitoring and inspection (full details in pharmacy manual). Data required for randomisation will be entered into REDCap directly. When the user confirms they are ready to

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randomise the necessary data will be piped into the CHaRT system which will automatically randomise, and the allocated pack ID will be piped back in to REDCap for the user to check (see section 12.3 for further details on data transfer between REDCap and CHaRT).

Sites will be required to answer data queries raised by ExeCTU in a timely manner within the trial database.

12.2. Source data

At pre-screening and baseline assessment, the primary data source will be the medical notes and source data worksheets.

Participant questionnaires will be completed for PROMs at each timepoint listed below:

- Baseline
- Week 12 follow up
- Week 26 follow up

PROMs will be complete electronically in REDCap while the participant attends for their in-person visits. If any technical issues occur, or if the participant requests it, paper copies of the questionnaire can be used by the site team and the data transcribed into the database.

If completed electronically the trial database will form the source data, otherwise the paper questionnaire will form the source data.

The source data for the randomised allocation and the pack ID(s) allocated to the participant will be in the CHaRT randomisation system.

Medical case notes containing source data or other trial-related information should be identified by a label (or equivalent for electronic notes, where feasible), e.g. “Keep until at least dd/mm/yyyy” where the date given is at least fifteen years after the end of the trial.

12.3. Data handling and record keeping

A Data Management Plan (DMP) will be created for the trial and will be updated throughout the trial as appropriate. Work instructions will be provided to the site teams on record keeping and data entry processes. Electronic systems will be validated, tested and documented before starting recruitment.

Any source data worksheets, paper questionnaires, paper consent forms and trial specific documents held by the site teams will be stored securely with access restricted and limited to research staff. If these are not stored in the ISF, a note to file will be placed in the ISF to indicate their location. Any source data recorded on paper questionnaires or source data worksheets will be transcribed into the eCRF.

Please see the data protection (section 15.5) for details on the electronic data capture system and how identifiable data will be stored.

12.4. Access to data

Participants will be asked to consent to representatives of the Sponsor, the University of Exeter or regulatory agencies (e.g. MHRA) accessing their data that is relevant to their participation in the trial.

Access to the data held at participating sites will be restricted to those who have a relevant purpose to access the data. Access will be granted to authorised representatives from the Royal Devon University Healthcare NHS Foundation Trust as Sponsor, as well as representatives from University of Exeter and regulatory agencies e.g. MHRA, for the purposes of auditing, monitoring and inspection of the trial.

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Data entered into the trial database (including unredacted uploads of paper consent forms and electronic consent forms) may be accessed by authorised members of the trial team at participating sites, ExeCTU and regulatory authorities (e.g. MHRA). Access to the database will be controlled by password protected individual user accounts. Delegated research staff will have access restricted by site, functionality and data that are appropriate for their location and role in the trial.

Exeter NIHR Clinical Research Facility at Royal Devon University Healthcare NHS Foundation Trust will be provided copies of participants informed consent forms to confirm the optional consent for research blood samples was provided.

Participants will also be asked to consent to data being shared with the following third-party providers:

- Centre for Healthcare Randomised Trials (CHaRT, University of Aberdeen) will provide the randomisation and IMP management system. CHaRT will not receive any identifiable information but will receive the participant's trial ID and eligibility criteria that are required for the randomisation. This system will also store the randomisation and IMP allocation data and a record of IMP pack statuses. Access to CHaRT's system will be restricted to password protected user accounts restricted by site, functionality and data appropriate to the user's role. Consent for this is required for a patient to participate in the trial.
- A company called Qureight Ltd will be provided copies of CT scans taken as standard of care, along with limited baseline demographic data. The CT scans and data will be pseudonymised with participant's trial ID. Consent for this is aspect of the trial is optional. An appropriate data sharing agreement will be put in place between the Sponsor and Qureight Ltd.

The above third parties will not be able to log into the trial database where the individual participant records are stored and the IMP manufacturer will not receive or hold any participant data.

12.5. Archiving

ExeCTU will support sites to prepare trial records for archiving in accordance with the Data Management Plan. The Sponsor is responsible for arranging appropriate archiving of the Trial Master File and CDMS data on conclusion of the trial.

Essential documentation will be archived by each participating site as per local procedures, including the Investigator Site File, consent forms (including copies of electronic consent forms, where relevant) and any source data worksheets. The site must notify ExeCTU and the Sponsor of their archiving arrangements and the Sponsor must be granted access to the archived documents/data upon request.

The essential documentation will be archived for a minimum of 15 years after the end of the trial. After 15 years, all personal identifiable data will be securely destroyed upon authorisation from the Sponsor. The anonymised dataset, including the anonymised CT scans, will be stored indefinitely (see section 15.10).

13. MONITORING, AUDIT & INSPECTION

A detailed monitoring plan will be agreed by the CI, ExeCTU and the Sponsor based on the trial risk assessment. The trial risk assessment and monitoring plan will be reviewed

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periodically throughout the trial and updated as necessary (e.g. after amendments to the trial protocol).

Monitoring will be led by ExeCTU and will be conducted remotely, centrally and potentially on-site as required. This will include monitoring of unredacted consent forms; paper consent forms, where used, will be uploaded (unredacted) to the trial database for this purpose. On-site monitoring may be conducted if triggered according to pre-defined criteria in the monitoring plan, or if concerns are raised by an individual with knowledge of the trial.

Sites will be expected to cooperate with monitoring procedures through timely provision of copies of requested documents and completion of self-audit checks where required. In the case of on-site monitoring visits, sites will be expected to provide space for the monitor(s) to work on the NHS Trust premises and provide access to all documents requested in the notification of monitoring visit letter. The PI or delegated member of the trial team must be available during on-site monitoring visits. The ExeCTU will provide sites with sufficient notice to prepare for a monitoring visit.

The Sponsor and/or regulatory authorities may audit or inspect the trial, including on-site visits at any time during the trial. All trial-related documents must be made available on request for monitoring and audit by the Sponsor or regulatory authorities.

The oversight committees will review data completeness, quality and accumulating safety data at agreed intervals throughout the trial.

14. PUBLIC AND PATIENT INVOLVEMENT

PPI has been central to the development of CHORUS. The trial team worked alongside Exeter patients in collaboration for pulmonary fibrosis research, the national charity Action for Pulmonary Fibrosis (APF) and British Pigeon Fanciers network to co-design this trial. Emphasis has been placed on understanding the needs and concerns of patients with FHP. This has helped to design an inclusive trial to ensure our research is relevant to these important groups.

An overarching Patient Advisory Group (PAG) led by the co-applicant APF PPI lead, will advise on trial processes throughout the trial. This may include inputting into patient-facing materials throughout the trial, co-producing the dissemination materials to be shared with participants and the public once the trial results are available and advising on the participant pathway and any potential recruitment barriers. We will encourage diversity within our PPI representatives and will invite participants for the PAG on a national level.

At the end of the trial, interested participants will be invited to help us develop participant focused trial literature with our PAG, which will be released on social media and our trial website.

Two co-applicant patient representatives sit on the TMG. At least one independent lay member will sit on the TSC.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Research Ethics Committee (REC) review & reports

The research will be performed subject to a favourable opinion from an NHS REC, HRA and MHRA, with subsequent appropriate local R&D departments Confirmation of Capacity & Capability for each participating site. Once the site has received the Sponsor green light, the trial can be activated at the site.

Ethics review of the protocol and other trial-related essential documents (e.g. PIS and consent form) will be carried out by a UK NHS REC. Any subsequent substantial

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amendments to these documents will be submitted to the REC, HRA and MHRA for approval prior to implementation. Amendments to the trial documents will also be submitted to the sites for information or approval as required, including confirmation of continued capacity and capability. The CI or delegate will work with sites to put the necessary arrangements in place to implement the amendment.

The REC will be notified of the end of the trial. If the trial is ended prematurely, this will be notified to the REC that approved the trial. A final report will be submitted to the REC after the end of the trial.

15.2. Peer review

This study is formally and strongly supported by the British Thoracic Society, following review by their Science & Research Committee. The proposal for this trial has been peer-reviewed through the NIHR peer-review process, which includes independent expert and lay reviewers.

15.3. Regulatory Compliance

Prednisolone is classed as an IMP and the trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA as well as favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol participants into the trial, the Sponsor, CI or delegate will ensure that appropriate approvals from regulatory authorities and the participating organisation are in place.

For any amendment to the trial, the CI or delegate, in agreement with the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment.

15.4. Protocol compliance

Non compliances are defined as follows:

- **Deviation:** A change or departure from the approved trial protocol, other key trial documents, GCP and/or applicable regulatory requirements that is **not likely** to affect the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.
- **Violation:** Failure to comply with the approved trial protocol, other key trial documents, GCP and/or regulatory requirements which has the **potential** to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.
- **Serious Breach:** A non-compliance that is **likely** to affect to a significant degree the safety or physical or mental integrity or rights of the trial participants, or the scientific value of the trial.

Trial personnel will be provided with a ‘non-compliance’ work instruction for guidance in the event that they become aware of a deviation, violation or suspected serious breach.

Non-compliances may be identified through routine or triggered monitoring, inspection by the regulatory authorities, by chance or by direct report to ExeCTU and/or the Sponsor by a member of the trial team or other party.

Non-compliances will be reported on a ‘Non-Compliance’ form on REDCap, which will be reviewed by ExeCTU on receipt. All reports of violations/suspected serious breaches will be forwarded by ExeCTU to the Sponsor within 24 hours of ExeCTU becoming aware of the

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event. The Sponsor will determine whether the event constitutes a serious breach and will manage onward reporting to the REC and MHRA, as required.

ExeCTU and the Sponsor will work with trial and site personnel to identify the cause of any non-compliances and put in place steps to mitigate them, as appropriate.

Non-compliances will be reviewed regularly by the CI and the TMG. Recurrent deviations will be discussed with the TMG and TSC, as appropriate.

If a non-compliance is also associated with an event which meets the criteria of an SAE or SUSAR this should also be reported in accordance with the pharmacovigilance section 9 of the protocol.

15.5. Data protection and patient confidentiality

Data will be collected and retained in accordance with the UK General Data Protection Regulation (UK GDPR), in conjunction with the Data Protection Act (DPA) 2018 and ICH GCP E6 R2 with regards to the collection, storage, processing, destruction and disclosure of personal information. End of trial results will be reported anonymously so that it will not be possible to identify any individual taking part in the trial.

Each participant will be assigned a unique participant ID number. Personal identifiable data and contact details will be collected and stored in the trial database as required for the research (e.g. to send follow-up or trial results). Fields which contain participant identifiers will sit on separate eCRFs to the rest of the data and will be restricted so that only authorised users can access the identifiable data. Uploaded unredacted paper consent forms and the unredacted eConsent forms will also be access restricted to authorised users of the database. Personal data will only be used for reasons relevant to the research as outlined in the participant information sheets and will be stored for 15 years after the end of the trial before being destroyed.

Data will be managed by ExeCTU following UK GDPR. Access to the CDMS (REDCap) web interface will be over Hyper Text Transfer Protocol Secure (HTTPS) / Transport Layer Security (TLS) version 1.2 as a minimum and it will be ensured that web traffic to and from the REDCap server is encrypted. REDCap will be hosted within University of Exeter Amazon Webservices (AWS) account. All data will be securely stored in AWS data centres in the UK. Amazon Relational Database Service (RDS) will be encrypted. Amazon RDS encrypted database instances use the industry standard AES-256 encryption algorithm to encrypt the data on the server that hosts the Amazon RDS database instances. The AWS global infrastructure is designed and managed according to security best practices as well as a variety of security compliance standards. AWS provides on-demand access to security and compliance reports and select online agreements through AWS Artefact. Standards include ISO 27001 and ISO 9001.

The management of randomisation data at CHaRT adheres to the UK GDPR, ensuring compliance with robust data protection measures. CHaRT will not receive any identifiable information but will receive the participant's trial ID and eligibility criteria that are required for the randomisation. CHaRT employs secure data transmission protocols, utilizing HTTPS/TLS 1.2 connections with industry-standard encryption algorithms to safeguard sensitive information during transfer. Data is securely stored in Aberdeen data centres, with off-site backups stored at Robert Gordon University. Access to data is strictly controlled through authentication mechanisms, ensuring only authorised users can access endpoints within the infrastructure. CHaRT conducts regular security audits and vulnerability assessments to identify and mitigate potential risks to data security. Additionally, all data transfers are logged to maintain a comprehensive record of activity. By implementing these measures, CHaRT

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ensures the secure management and transfer of randomisation data, maintaining the integrity and confidentiality of sensitive information in accordance with UK GDPR requirements.

Only PI or their authorised delegates who are suitably qualified and trained will access the patients' medical notes to gather the required information for the trial. Investigators will hold substantive or honorary contracts with the NHS Trust at which the patient is recruited and will therefore be bound by a duty of confidentiality.

Data collected at sites on paper such as consent forms (including any printed copies of eConsent forms) will be stored securely and archived at site. Any electronic copies of the eConsent form (downloaded from REDCap) held at sites will be stored and archived in accordance with local policy and access restricted to authorised members of the research team.

The data controller for the trial is the Sponsor, Royal Devon University Healthcare NHS Foundation Trust.

15.6. Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The CI and co-lead do not have any competing interests. Members of the TSC and DMC will complete conflict of interest forms declaring any competing interests; these will be filed in the TMF. PIs will be provided with a PI declaration form as part of the model non-commercial agreement in which competing interests will be identified.

15.7. Indemnity

This is an NHS-sponsored research trial. For NHS-sponsored research if there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

15.8. Amendments to the trial protocol

Amendments to the trial documents will be approved by the Sponsor prior to submission to the HRA/REC/MHRA. The Sponsor will decide if an amendment is substantial or non-substantial following HRA guidance.

All substantial amendments and relevant non-substantial amendments will be discussed by the TMG and with the PAG if appropriate. The CI will be responsible for the final decision on making an amendment to the protocol. The approval of the TSC chairperson will be sought for substantial amendments to the protocol in advance of submitting them to the REC/MHRA/HRA, and if necessary, a meeting of the TSC will be convened to discuss the amendment. The funder representative will be notified of relevant substantial amendments in advance of submission, and a full list of all substantial and non-substantial amendments will be provided as part of regular funder reports.

All amendments will be submitted to the NHS REC that issued a favourable opinion (if appropriate), the HRA and/or the MHRA following the appropriate amendment process in place at the time of submission. Amendments will be communicated by ExeCTU to R&D departments, PIs and research teams at participating sites as soon as possible upon receipt of approval to do so from the HRA. The CI or delegate will inform the trial registry of changes to the trial.

The protocol version history will be recorded on the protocol.

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15.9. Post-trial care

Trial participation will end for a participant after their week 35 End of Study follow-up. After this point, patient participants will continue to receive standard NHS care with no special arrangements made in relation to the trial.

15.10. Access to the final trial dataset

Anonymised research data and outputs will be stored in a research repository hosted by one of the collaborating organisations (Sponsor and/or University of Exeter) to facilitate access to, and the impact of our research. All future research proposals must obtain the appropriate ethical and regulatory approvals. The details will be outlined in the Data Management Plan (DMP). All future research proposals must obtain the appropriate ethical and regulatory approvals.

16. DISSEMINATION POLICY

16.1. Dissemination policy

The findings will be disseminated by usual academic channels, i.e. the trial team aim to present findings at international meetings, as well as by peer-reviewed publications (including a full report to the NIHR Health Technology Assessment programme) and through patient organisations and newsletters to patients, where available. The results will be communicated to the Royal College of Medicine, Society for Acute Medicine, NICE and NHS England to inform national guidelines.

Our patient groups will guide us how to inform patients of the results, using social and traditional media. The results will be posted on the publicly available registry (ISRCTN).

On recruitment, all participants will be invited to be updated on the trial progress and findings. A trial website and social media accounts will be maintained to share updates on recruitment, results, and general trial information.

The trial protocol will be published in an open access academic journal.

16.2. Authorship eligibility guidelines and any intended use of professional writers

Authorship on relevant publications will be offered in line with The International Committee of Medical Journal Editors guidance. This will include contributors to trial development (e.g. grant funding, protocol development), running the trial (e.g. recruiting patients, being a lead investigator for sites) and other aspects of trial design/analysis (e.g. statistical and methodological work).

The trial team do not plan to engage the use of professional writers for this trial.

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18. APPENDICES

Appendix 1 – Power Calculations

Table 1: Sample size scenarios showing detectable between-group difference with 90% power (two-sided 5% significance level) with varying assumptions for number of participants recruited, follow-up rate and standard deviation of change in FVC. Calculations based on group sequential design with one interim analysis (two total looks including the final analysis)

	% of Participants with Primary Outcome	Standard Deviation of FVC Change (ml)	Detectable Between-Group Difference in Change in FVC (ml)	Detectable Standardised Effect Size
Total Number of Participants Recruited: N = 222 (111 per Allocated Group)				
Base case	**90%**	**125**	**58**	**0.464**
Vary % with Primary Outcome	95%	125	56	0.448
	85%		59	0.472
	80%		61	0.488
Vary SD	90%	100	46	0.460
		150	69	0.460
		175	81	0.463
Total Number of Participants Recruited: N = 200 (100 per Allocated Group)				
Vary % with Primary Outcome	95%	125	59	0.472
	90%		61	0.488
	85%		63	0.504
	80%		65	0.520
Vary SD	90%	100	49	0.490
		150	73	0.487
		175	86	0.491
Total Number of Participants Recruited: N = 180 (90 per Allocated Group)				
Vary % with Primary Outcome	95%	125	63	0.504
	90%		64	0.512
	85%		67	0.536
	80%		68	0.544
Vary SD	90%	100	52	0.520
		150	77	0.513
		175	90	0.514