Trial Title: Delivering personalised care in the management of exacerbations of chronic obstructive pulmonary disease: A multi-centre randomised clinical trial

Internal Reference Number / Short title:

STudying Acute exaceRbations and Response: The COPD STARR 2 study

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Chief Investigator:	Professor Mona Bafadhel
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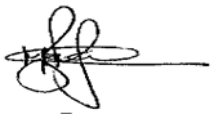
Chief Investigator Signature:



There are no conflicts of interest to declare

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

TABLE OF CONTENTS

KEY TRIAL CONTACTS

Chief Investigator	Professor Mona Bafadhel, mona.bafadhel@ndm.ox.ac.uk, Respiratory Medicine Unit, NDM Research Building. Old Road Campus, University of Oxford, OX3 7FZ. UK. Tel: +44 1865 612898
Research Nurses	Mrs Helen Jeffers RGN Research phone +44 7554 436726 Mrs Joanne Davies RGN Research phone +44 7769 280289
Statistical advisor	Susan Dutton: Susan.dutton@csm.ox.ac.uk Oxford Clinical Trials Research Unit. University of Oxford
Sponsor	University of Oxford Clinical Trials and Research Governance, Joint Research Office, Joint Research Office, Boundary Brook House, Headington, Oxford, OX3 7GB , ctrg@admin.ox.ac.uk
Trial Managers	Hania Piotrowska; email: hania.piotrowska@ouh.nhs.uk, Tel: 01865 225552 Oxford Respiratory Trials Unit, University of Oxford, Churchill Hospital, Oxford, OX3 7LE
Data Manager	Jack Quaddy: Jack.quaddy@ouh.nhs.uk Oxford Respiratory Trials Unit, University of Oxford, Churchill Hospital, Oxford, OX3 7LE. Tel: 01865 223749

1. SYNOPSIS

Trial Title	Delivering personalised care in the management of exacerbations of chronic obstructive pulmonary disease: A multi-centre randomised clinical trial	
Internal ref. no. (or short title)	The COPD STARR 2 Study	
Trial Design	Multi centre, double blind, placebo controlled	
Trial Participants	Adults >40, Female and Male, with diagnosis of COPD	
Planned Sample Size	228 exacerbation events	
Treatment duration	2 weeks	
Follow up duration	12 months	
	Objectives	Outcome Measures
Primary	To evaluate the efficacy of blood-eosinophil directed corticosteroid therapy using near-patient testing, compared to current standard practice during an exacerbation of COPD	1. Proportion of treatment non-responders, defined as those needing re-treatment, hospitalisation or death at 30 and 90 days
Secondary	To evaluate quality of life, symptoms, lung function and healthcare utilisation in a blood-eosinophil directed corticosteroid therapy arm	2. Change from baseline in CAT health status 3. Change from baseline in VAS symptom scores 4. Change from baseline in EQ-5D 5. Change from baseline in FEV_1 6. Frequency of moderate and severe exacerbations
Exploratory	To evaluate stability of blood eosinophils and mediators	7. Change in eosinophil levels 8. Inflammatory mediatory levels
Investigational Medicinal Product(s)	Prednisolone and Placebo	
Formulation, Dose, Route of Administration	30mg Prednisolone taken orally one tablet daily for 14 days	
Non-investigational Medicinal Product	Doxycycline	
Formulation, Dose, Route of Administration of NIMP	200mg on day 1 and 100mg taken daily for the following 6 days	

2. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CAT	COPD assessment tool
CI	Chief Investigator
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C reactive protein
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
EQ5D	EuroQoL-5D
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GMP	Good medical practice
GP	General Practitioner
HADS	Hospital anxiety and depression scale
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical research council
NCR	No carbon required
NDM	Nuffield department of clinical medicine
NHS	National Health Service
NIMP	Non-investigational medicinal product
NNT	Number needed to treat
OCTRU	Oxford clinical trials research unit
OR	Odds ratio

ORTU	Oxford respiratory trials unit
PEF	Peak expiratory flow
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PRO	Patient reported outcome
QOF	Quality outcomes framework
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	tuberculosis
TMF	Trial Master File
TSG	Trials Safety Group
TSI	Trial Specific Instruction
VAS	Visual analogue score

3. BACKGROUND AND RATIONALE

Chronic obstructive pulmonary disease (COPD) is associated with significant morbidity and mortality [1] negatively affecting quality of life and associated with lung function decline [2]. It affects adults and is largely caused by cigarette smoking in the developed world. It is predicted to be the 3rd leading cause of death by 2020 affecting over 250 million people worldwide [3]. COPD is characterised by progressive airflow obstruction and punctuated by frequent periods of worsening in respiratory symptoms and function associated with significant impact on quality of life. These episodes are termed exacerbations and represent a large burden on healthcare, accounting for 15% of all U.K acute hospital admissions, 1 million hospital bed days and an estimated annual NHS expenditure of approximately £500 million [4]. In the U.K, more than 1.4 million GP consultations annually are attributable to COPD exacerbations. It is estimated that there are 130,000 hospitalised exacerbations of COPD annually and approximately 75% of these have been treated by the GP within 4 weeks prior to the hospital admission [4]. A single acute episode of COPD requiring hospitalisation costs £1,500 [5] and projected treatment failure costs accumulate to over £145 million annually. At present there is limited evidence to understand why patients seen and treated by the GP fail treatment within 30 days and require further treatment and/or hospital admission.

Current treatment strategies using corticosteroids and antibiotics

Current COPD exacerbation treatment strategies rely on oral corticosteroids and antibiotics but this is in a 'one size fits all' approach. Patients are treated with systemic corticosteroids (30mg prednisolone once a day for maximum of 14 days) and/or antibiotics (amoxicillin or doxycycline, if penicillin allergic, for 5 days). Furthermore the evidence for the use of corticosteroids and antibiotics during COPD exacerbations is weak [6,7] and both treatments can potentially cause harm [8-10]. The number needed to treat (NNT) to prevent one treatment failure with prednisolone during an exacerbation of COPD is 10. However the number needed to harm (NNH) is 5 [6] with over 50% of patients developing significant hyperglycemia [11]. In a Cochrane review the evidence of systemic corticosteroids and antibiotics during exacerbations, the improvements were short term without mortality benefits[6,7]. Side effects included hyperglycemia (odds ratio (OR) 4.95; 95% CI 2.47 to 9.91) and diarrhoea (OR 2.62; 95%CI 1.11 to 6.17). Evidence has focused on severe or hospitalised exacerbations of COPD and despite their widespread use there are no studies investigating outcomes in exacerbations presenting to the GP. Pathogens such as bacteria and viruses are believed to be the major underlying cause of COPD exacerbations [12,13]. In primary care, sampling for virus or bacteria at the onset of an exacerbation is not performed and guidance for the prescription of antibiotics is based on symptoms and sputum purulence [14] although confounded by the presence of bacterial colonisation[15].

The eosinophil as a biomarker in COPD exacerbations

Trends have advocated the characterisation of COPD phenotypes which relate to clinically meaningful outcomes such as symptoms, exacerbations and responses to treatment in the management of COPD [16]. The presence of a sputum eosinophilia in stable COPD has been repeatedly associated with a positive clinical response (FEV_1 and symptoms) following treatment with oral corticosteroids [17-19]. A sputum eosinophilia is detected in up to 40% of COPD [20], but processing is time consuming and requires specialist skills [21]. We have previously determined and validated the blood eosinophil count as the best surrogate for a sputum eosinophilia during COPD exacerbations [22,23]. Furthermore, it has been observed that the blood eosinophil count is a predictor of mortality in severe exacerbations [24] re-admissions[25] and length of hospital stay[26] and the CRP is predictive of a treatment failure in mild to moderate exacerbations [27]. The combination of these independent findings suggests that the blood eosinophil count can be used as a biomarker to determine treatment with oral steroids and will improve the evidence base as there is a current paucity of randomised clinical trials in primary care in mild or moderate exacerbations of COPD to support the practice of personalised corticosteroid therapy at the onset of an exacerbation.

Directed treatment using near-patient testing

The use of near-patient testing in primary care will characterise patients with COPD and inform to guide effective and personalised treatment with reductions in treatment failure rates, improvements in health and reductions in adverse events associated with inappropriate and excessive corticosteroid and antibiotic therapy. Currently available systems include the HemoCue ® 5-point differential cell count system which accurately and rapidly (within 2 minutes) determine the eosinophil count finger-prick sampling. This diagnostic is currently used in neonatology, Emergency Departments (ED) and at Mount Everest Base Camp [28-30]. It is thus conceivable that this could be used in primary care to deliver a randomised control trial to demonstrate that stratified medicine approaches in the management of COPD exacerbations are superior to standard therapy.

Hypothesis

A personalised stratified treatment approach using the peripheral eosinophil count, from near-patient testing, to direct systemic corticosteroids, during an exacerbation of COPD, is superior to current standard 'one size fits all' treatment strategies in the primary care setting.

Investigational medicinal product

The IMP in this study is prednisolone and is part of current clinical practice. Prednisolone is an anti-inflammatory and given in short durations (≤2 weeks duration) orally for its systemic action at the onset of an exacerbation in COPD. Participants will receive a dose of prednisolone that is not different to usual practice (see figure 1).

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Time point(s) of evaluation
Primary Objective To evaluate the efficacy of blood-eosinophil directed corticosteroid therapy using near-patient testing, compared to current standard practice during an exacerbation of COPD	Proportion of treatment non-responders, defined as those needing re-treatment, hospitalisation or death at 30 and 90 days	Day 30 Day 90
Secondary Objectives To evaluate quality of life, symptoms, lung function and healthcare utilisation in a blood-eosinophil directed corticosteroid therapy arm	i) Change from baseline in CAT health status ii) Change from baseline in VAS symptom scores iii) Change from baseline in EQ-5D iv) Change from baseline in FEV_1 v) Frequency of moderate and severe exacerbations	Day 14, 30 and 90 (for outcomes i-iv) 12 months (for outcome v)
Exploratory Objectives To evaluate the stability of blood eosinophils and mediatory levels	i) Change in blood eosinophil counts ii) Change in inflammatory mediators	i) At all visits (except 12 months) ii) Stable state and exacerbation

5. TRIAL DESIGN

Study design: Double-blind placebo controlled randomised clinical trial

Study setting: Primary care GP practices

Participants: Adults ≥40 years with COPD

Intervention: At exacerbation randomised to 'standard therapy' or 'blood eosinophil directed therapy'. Standard therapy will be prednisolone and antibiotic therapy. Blood eosinophil directed therapy will be prednisolone and/or antibiotic therapy.

Investigational medicinal product: Prednisolone or placebo equivalent

Participation duration: Study entry at stable state or during an exacerbation. Randomisation at exacerbation. IMP treatment period 14 days. Post treatment follow-up visits at days 14, 30 and 90. Stable state and randomisation visit duration maximum 60 minutes. Follow-up visits at days14, 30, and 90 maximum duration 30 minutes. Participants may be re-randomised and followed up if they have further exacerbations after the 30 day visit.

Data collection: Demographic and exacerbation clinical data including duration of symptoms, past medical history, medication history and exacerbation history will be collected. Blood eosinophil tests will be collected by pin-prick testing using the HemoCue ®; lung function using spirometry; and symptoms and quality of life using questionnaires. Serum will be collected at visits.

Study schedule: Following consent, there will be a stable and/or exacerbation randomisation visit; exacerbation follow-up visits at days 14, 30 and 90. Medical record interrogation at 12 months

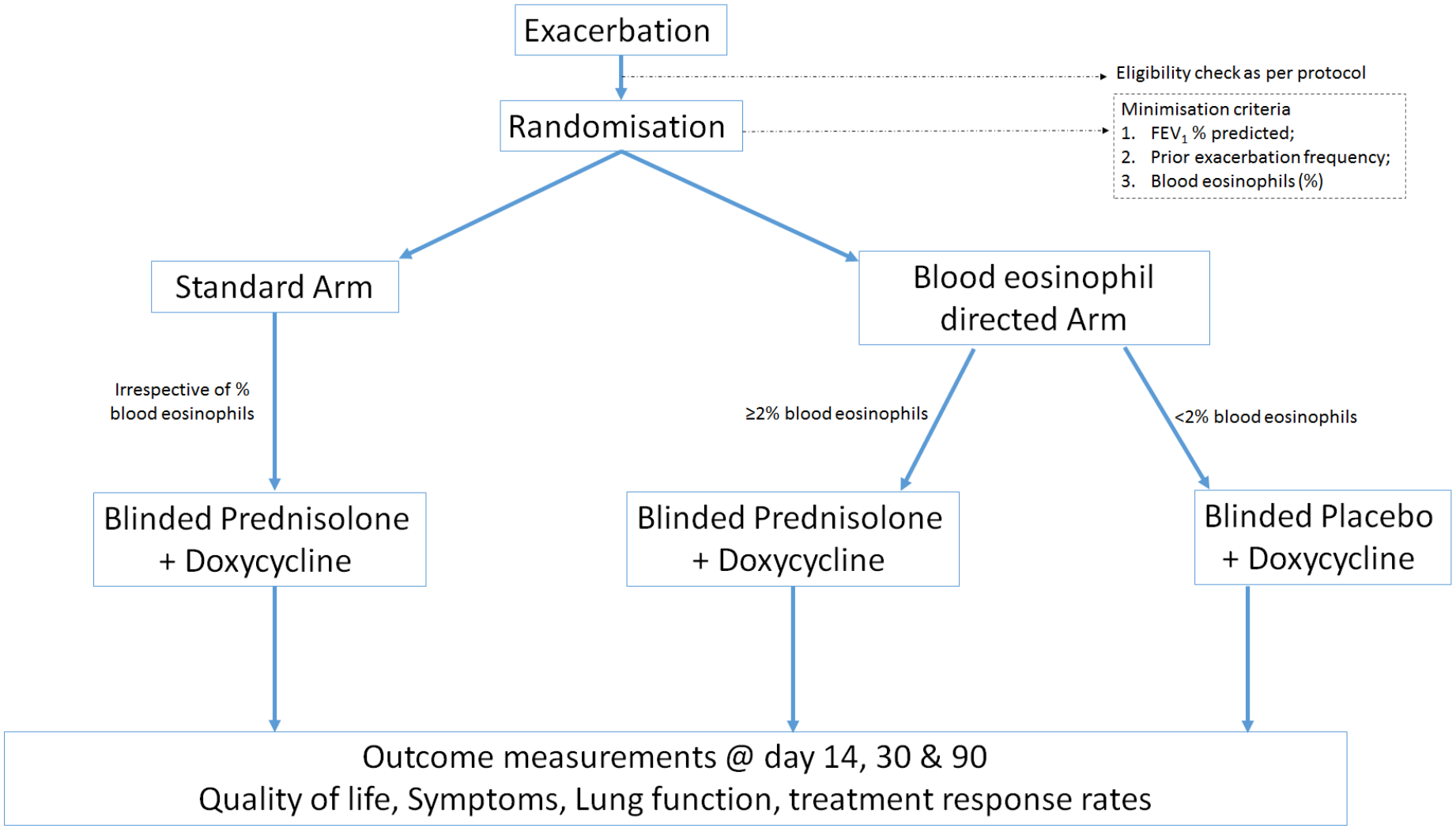
Primary objective: To evaluate the efficacy of blood-eosinophil directed corticosteroid therapy using near-patient testing, compared to current standard practice during an exacerbation of COPD.

Secondary objective: To evaluate quality of life, symptoms, lung function and healthcare utilisation in a blood-eosinophil directed corticosteroid therapy arm.

Exploratory objective: To evaluate stability of eosinophil counts and mediator levels

Sample size: 228 exacerbation events

Study duration: 12 months data collection



6. PARTICIPANT IDENTIFICATION

6.1. Trial Participants

Adult participants with COPD, of any severity aged 40 and over.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial.
- Male or Female, aged 40 years or above.
- Diagnosed with COPD (primary or secondary care diagnosis) with spirometric confirmation of airflow obstruction (FEV_1/FVC ratio <0.7).
- A history of at least 1 exacerbation in the previous 12 months, requiring systemic corticosteroids and/or antibiotics.
- Current or ex-smoker with at least a 10 pack year smoking history
- In the opinion of the research staff, is able and willing to comply with all trial requirements.

6.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- History of atopic childhood asthma
- Current history of primary lung malignancy or current active pulmonary TB
- Clinically relevant disease or disorder (past or present) which in the opinion of the investigator may either put the subject at risk because of participating in the study or may influence the results of the study or the subject's ability to participate in the study.
- Any clinically relevant lung disease, other than COPD considered by the investigator to be the primary diagnosis. For example mild-to-moderate bronchiectasis is acceptable in addition to COPD unless the bronchiectasis is considered to be the primary diagnosis.
- An alternative cause for the increase in symptoms of COPD that are unrelated to an exacerbation such as i) suspicion or clinical evidence of pneumonia; ii) high probability and suspicion of pulmonary embolism; iii) suspicion or clinical evidence of a pneumothorax; iv) primary ischaemic event – ST or Non ST elevation myocardial infarct and left ventricular failure [i.e. not an exacerbation of COPD]
- A known allergy to the IMP (prednisolone), NIMP (doxycycline) or to any of the constituents of the placebo
- Patients on maintenance corticosteroids (prednisolone, hydrocortisone, fludrocortisone)
- Known adrenal insufficiency
- Currently enrolled in another CTIMP trial and receiving an intervention as part of the trial.
- Pregnant and breast-feeding women.

7. TRIAL PROCEDURES - VISITS

	Visits					
	Stable €	Exacerbation § ¥	Day 14	Day 30	Day 90	12 months*
Consent	✓	✓				
Eligibility check	✓	✓				
Demographics δ	✓	✓				
Medical history δ	✓	✓				
COPD history δ	✓	✓				
Medication history δ	✓	✓				
Exacerbation details		✓				
Randomisation		✓				
Administration of IMP		✓				
Spirometry	✓	✓	✓	✓	✓	
Pin prick blood testing	✓	✓	✓	✓	✓	
Venous blood sampling	✓	✓	✓	✓	✓	
Urine testing		✓	✓			
Questionnaires	✓	✓	✓	✓	✓	
Medical note review	✓	✓				✓
Assessment of outcome measures			✓	✓	✓	✓
SAE/AE reporting		✓	✓	✓	✓	

*€ can be undertaken before or after exacerbation visit, if post exacerbation to be undertaken at additional visit 6 weeks free from an exacerbation; § exacerbation to day 14 visit – self administration of IMP; ¥ exacerbation to day 30 visit – self completion of symptom diary card; δ details can be collected at stable or exacerbation visit; * review of medical notes only*

7.1. Recruitment

Within primary care, as part of the quality and outcomes framework (QOF) for managing long term common and chronic conditions, GPs annually perform spirometry and identify patients with respiratory disease. Within this identification procedure, all primary care practices nationally have COPD registers. At the selected practices (within the Thames Valley region) there are over 800 patients with COPD on the registers. This will identify COPD participants immediately, with invitation letters and patient information sheets sent jointly from the study team and the GP surgery. Screening for suitability will be available directly from GP medical records for the primary care COPD registered patients. All GP practices have web based advertising and televisual aids in waiting rooms and adverts will be placed on these interfaces; and can contact the research team if they are interested in the study. If following this contact the research team considers the participant to be eligible for the study, the research team will contact the clinical team to confirm eligibility for the trial before sending out a patient information sheet. Participants will be contacted after they have been sent the patient information sheets to review if they have any questions and whether they are interested in participating. All visits will be undertaken at the local GP practice.

Participants can be recruited for a stable visit, which is free from exacerbation symptoms and randomised at the exacerbation visit upon contact. Participants can also be recruited directly at an exacerbation visit and randomised.

7.2. Screening and Eligibility Assessment

At the screening visit participants will be given the opportunity to ask the research staff any questions they have about the study prior to providing informed written consent. Participants will be informed that they can withdraw from the research project at any time without prejudice to further care. No pre-specified screening procedures are required for subject recruitment. Upon provision of consent investigators will confirm eligibility and study assessments will be undertaken. Participants may enter the randomisation visit, if there is an associated exacerbation, or the stable visit.

7.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed. Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking

part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant, a copy will be filed in the participant's medical notes and a copy will be sent to the central coordinating centre. The original signed form will be retained at the trial site.

7.4. Randomisation, blinding and code-breaking

Randomisation will occur at the onset of an exacerbation. Randomisation of participants will be into a standard therapy arm or a blood-eosinophil directed therapy arm (see figure 1). A participant can be randomised up to 4 times if they experience repeat exacerbations.

Randomisation

Consented participants will be randomised (1:1) to standard or directed therapy using the centralised computer randomisation service RRAMP (https://rramp.octru.ox.ac.uk) provided by the Oxford Clinical Trials Research Unit (OCTRU). Randomisation will be undertaken using stratification to ensure a balanced allocation across treatment groups, stratified by eosinophil count, disease severity as measured by FEV at baseline and prior exacerbation history. The randomisation schedule will be created by the unblinded OCTRU statistician and transferred securely to the IMP manufacturers, Tiofarma BV, on behalf of WGK, who will package and label the IMP according to this schedule.

Blinding

All participants will be blinded to prednisolone therapy and receive open-labelled antibiotics (Doxycycline 200mg for the first day and 100mg once per day for the following 6 days). Participants in the 'blood eosinophil directed' study arm will receive antibiotic (doxycycline, open labelled) and IMP (prednisolone or placebo) dependent on the blood eosinophil count at the randomisation (exacerbation visit). Participants in the 'standard therapy' study arm will receive IMP (prednisolone) and antibiotic (doxycycline, open labelled) irrespective of the blood eosinophil count at randomisation. The randomisation and provision of codes will be performed according to SOP (operated by OCTRU, schedule design by statistician, held at OCTRU).

Code breaking

If unblinding is necessary then this will be supplied for a single participant and can be accessed using the RRAMP online system. The randomisation service (RRAMP) provides a facility for emergency unblinding of treatment allocation which can be accessed by the local PI. All emergency unbinding will be at the discretion of the local investigators, when clinically indicated for the safety of the patient. Investigators should refer to the trial specific instructions (TSI) for the emergency unblinding procedure. Non-emergency unblinding can be requested via the RRAMP system and will require approval by the Chief Investigator.

7.5. Study Assessments

Study assessments will be performed within primary care by the research study team. The following assessments may occur at the study visits.

Eligibility check: Inclusion and exclusion criteria will be checked against the participant's medical notes and with the participant during the visit. This responsibility will be delegated by the PI to a member of the research team.

Demographic history: Participant demographics including age, smoking history and past COPD medical history will be collected.

Medication history: Full medication history will be collected, including the use of as required and over the counter medication. Any drug allergy will be documented and dates of flu vaccination, S. pneumoniae and H. influenzae B vaccinations will be recorded from medical records.

Past medical history: Full medical history will be collected from the participant and from the medical notes.

COPD diagnosis history: The age of onset and age of diagnosis of COPD symptoms will be recorded from the participant and from the medical records.

Past exacerbation history: The frequency of exacerbations, including those requiring hospitalisation in the previous 12 months will be captured from participant recollection and from the medical records. Medication prescribed at each exacerbation event (if available) from medical records will be captured.

Exacerbation history: The current history of the exacerbation, including duration of symptoms and treatment history will collected by questioning. The severity of the exacerbation will be recorded according to Anthonisen criteria[14] with increased symptoms of breathlessness, sputum production and sputum purulence will be used as per GOLD[31] definition. The Anthonisen criteria for exacerbation as follows: Type 1 – Three major symptoms; Type 2 - two major symptoms; Type 3 – One major and one minor symptom. The major symptoms are i) Increased breathlessness; ii) increased sputum production; or iii) increased sputum purulence. The minor symptoms are iv) Upper respiratory tract infection in the previous 5 days; v) fever without apparent cause; vi) increased wheeze; vii) increased cough; viii) increase in respiratory or heart rate 20% above baseline.

Questionnaires: Patient reported outcome measures (PRO's) will be sought to specifically test symptoms, health status, quality of life and any associated depression and anxiety. This will include the Medical Research Council dyspnoea scale (MRC); Visual analogue score (VAS) [32]; COPD Assessment Tool (CAT) [33]; the Hospital Anxiety and Depression Scale (HADS)[34] and the EuroQol 5D[35]. Participants will be asked to complete a daily diary (using the VAS tool, for the duration of 30 days) for assessment of symptoms and recovery following treatment. Instructions to use these questionnaires will be given to all participants. Each of these questionnaires are validated to be self-completed for ease of use. All research staff undertaking any assessments and procedures will be trained to use the equipment and perform the questionnaires to determine patient reported outcomes.

Near-patient point of care testing procedures: Approximately 5 drops of blood (up to a maximum of 10 drops) will be taken for measurement of peripheral blood eosinophil counts, glucose and CRP levels. A urine sample for testing of glycosuria will be performed immediately. All samples will be discarded.

Lung Function: Spirometry will be performed to determine the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC) according to standard ATS/ERS criteria[36].

Venous blood sampling: Using a fully sterile technique, a blood test will be performed to measure inflammation. All participants consenting to trial sample collection will have a maximum of 20mLs of blood taken at each visit. Collected blood will be centrifuged immediately and serum/plasma will be aliquoted into fully anonymised barcoded tubes. Anonymised samples will be then be securely transported to the John Radcliffe Hospital and stored at the Respiratory Medicine Laboratory (John Radcliffe Hospital), under the HTA licence, at -80˚c for exploratory outcome analysis and for future use subject to ethical approval. There will be separate instructions detailing the sample handling process for this study.

Further details of the procedures are found in Appendix B.

7.6. Study visits

7.6.1. Stable visit

This is a scheduled visit and occurs when the participant is 6 weeks free from an exacerbation. This visit can occur immediately following informed consent or following randomisation at a subsequent later date. The duration of this visit will be a maximum of 60 minutes. The assessments that will be conducted are:

- *Eligibility check*
- *Demographic history (can be collected at stable or exacerbation visit)*
- *Medication history (can be collected at stable or exacerbation visit)*
- *Past medical history (can be collected at stable or exacerbation visit)*
- *COPD diagnosis history (can be collected at stable or exacerbation visit)*

- *Past exacerbation history (can be collected at stable or exacerbation visit)*
- *Questionnaires*
- *Near-patient point of care testing procedures*
- *Lung Function*
- *Venous blood sampling*

7.6.2. Exacerbation visit (Randomisation)

This is the randomisation visit, where IMP will be administered. The exacerbation visit can occur immediately following informed consent if the patient is recruited during an exacerbation. The duration of this visit will be a maximum of 60 minutes. An exacerbation is defined according to guidelines as the following 'an event in the natural course of the disease characterised by a change in the patients baseline dyspnoea, cough and/or sputum that is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication in a patient with underlying COPD.' Only treatment naïve exacerbations, captured within working hours Mon-Fri will be randomised. As patients with COPD commonly experience on average two exacerbations per year, participants can be re-randomised if they experience a further exacerbation which meets the eligibility criteria and they consent to continue. This re-randomisation can occur in participants who have completed the study (attended a Day 90 visit), or participants who have completed a Day 30 visit. A maximum of 4 exacerbations per participant can be randomised to the study arms described in Figure 1 and the repeat exacerbation visit will take approximately 30 minutes.

The nature of an exacerbation and according to current NICE standards, patients do not have to see a medically qualified physician to start treatment with prednisolone and/or antibiotics. Firstly, the majority of patients with COPD have 'standby treatment packs of prednisolone and antibiotics' at home with encouragement to take if their symptoms necessitate it; secondly, patients are informed to phone the GP surgery or practice nurse to ask for a prescription for which they then pick up later; and thirdly they can contact their community respiratory nurses or see the practice nurse who then often prescribes treatment. In light of this, for the purpose of this study, the Principal Investigator at site will delegate the responsibility of confirming an exacerbation to the research nurses to be able to proceed with the randomisation. Access to a medically qualified physician or the PI will be available at sites should this be required by the designated research nurse.

The assessments that will be conducted at this visit are:

- *Eligibility check*
- *Demographic history (if no prior history available)*
- *Medication history (if no prior history available)*
- *Past medical history (if no prior history available)*
- *COPD diagnosis history (if no prior history available)*
- *Past exacerbation history (if no prior history available)*
- *Exacerbation history**
- *Dispensing of IMP**
- *Questionnaires**
- *Near-patient point of care testing procedures**
- *Lung Function**
- *Venous blood sampling**

**Only these following study assessments will need to be collected in participants attending a repeated exacerbation visit, which fulfils the randomisation eligibility criteria.*

7.6.3. Follow-up visit at day 14 (+/- 2 days)

This is the first follow-up visit. The duration of this visit is 30 minutes. The following assessments will be completed:

- *Questionnaires*
- *Near-patient point of care testing procedures*
- *Lung Function*
- *Assessment of outcome measures*
- *Assessment of AE*

- *Assessment of trial drug compliance*
- *Venous blood sampling*

7.6.4. Follow-up visit at day 30 (+/- 7 days)

This is the second follow-up visit. The duration of this visit is 30 minutes. The following assessments will be completed:

- *Questionnaires*
- *Near-patient point of care testing procedures*
- *Lung Function*
- *Assessment of outcome measures*
- *Assessment of AE*
- *Venous blood sampling*

7.6.5. Follow-up visit at day 90 (+/- 7 days)

This is the third follow-up visit. The duration of this visit is 30 minutes. The following assessments will be completed:

- *Questionnaires*
- *Near-patient point of care testing procedures*
- *Lung Function*
- *Assessment of outcome measures*
- *Assessment of AE*
- *Venous blood sampling*

All effort should be made to ensure that follow ups at day 14, 30 and 90 are face to face with the research nurses within the surgeries. A telephone follow up will only be conducted due to extenuating circumstances.

If a participant exacerbates a second (or third) time prior to the 90 day follow up visit and is re-randomised to the study then they will not have the 90 day follow up visit post the first randomisation. The timeline of follow-up visits will start again following the most recent exacerbation. For data purposes, patients will keep their initial ID and if an exacerbation occurs the pre-fix will change (1, 2, 3 or 4) according to the exacerbation.

7.7. Notes Review

This is a medical note review, to determine annual exacerbation rate, and does not require any study assessments of participants. For most participants, this review at the latest will be 12 months post the last randomisation, however if the participant dies before this point, the notes review will be undertaken at that point and the trial team will not wait until 12 months.

7.8. Discontinuation from Trial Treatment and Withdrawal

In the event of withdrawal or discontinuation from trial treatment, due to non-treatment response, unblinding, or clinically indicated, i.e. that which is felt necessary by the local PI or responsible clinician then all subsequent treatment and care will be provided by the clinical team (GP or other) and participants will be asked to omit taking IMP and return to the research team for IMP accountability. Subsequent study visits will be continued, unless the patient withdraws their consent to do so.

Each participant has the right to withdraw their consent to continue from the study at any time. The reason for withdrawal will be asked and this will be recorded in the CRF, but the participant is not obliged to give a reason. In the event of a withdrawal, no further data will be collected; data already collected will be included in the final analyses. In the event of a discontinuation from the trial during the 14 days following randomisation, participants will be asked to stop taking IMP and return remaining IMP to the research team for accountability.

7.9. Definition of End of Trial

The end of trial is when all have had their final notes review – which for most participants will be at 12 months after final randomisation and the trial has had its analysis completed.

8. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

8.1. IMP Description

The investigational product is prednisolone (or matched placebo, made up of Lactose, Microcrystalline Cellulose, Carboxymethylcellulose and Magnesium Stearate). At the randomisation (exacerbation) visit, participants in the blood eosinophil directed study arm will receive either blinded prednisolone at a dose of 30mg once per day or matching placebo for 14 days. Participants in the standard therapy study arm will receive blinded prednisolone at a dose of 30mg once per day for 14 days. Each participant will receive 1 box per randomisation of IMP or placebo; each filled with 15 tablets (3 blister packs of 5 tablets) and advised to take the IMP orally, 1 tablet per day for 14 days, with a glass of water in the morning with food. There is an overage of 1 tablet in the box in case a tablet is lost by the participant during an exacerbation. Instructions on taking the IMP will be on the drug packaging and will also be verbally given by the research team at the exacerbation visit.

The investigational product, prednisolone or placebo, will be packed and labelled by Tiofarma BV on behalf of WGK Ltd Pharmaceutical Manufacturing Unit, according to current EU Good Manufacturing Practice (GMP) guidelines. The label will fulfill GMP Annex 13 requirements and/or local regulatory requirements. The investigational product (box), may be labelled with the following requirements:

- Name, address, telephone number of the sponsor
- Name of the Investigator(s)
- Subject Initials and study number
- Pharmaceutical dosage form, quantity of dosage units, and name and strength of the investigational product
- Quantity of product
- “for clinical trial use only”
- Route of administration
- Expiry date
- Storage conditions
- “keep out of reach and sight of children”
- Batch and lot number
- Address of pharmacy manufacturing unit

Undesirable effects of prednisolone

A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown. The incidence of predictable undesirable effects, including hypothalamic-pituitary adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see Section 4.4 'Special warnings and special precautions for use'). Assessment of undesirable effects is based on the following frequency groupings:
Very common: ≥1/10; Common: ≥1/100 to <1/10; Uncommon: ≥1/1,000 to <1/100; Rare: ≥1/10,000 to <1/1,000; Very rare: <1/10,000; Not known: cannot be estimated from the available data.

8.2. Non investigational medicinal product (NIMP) description

The NIMP in this study will be doxycycline. This is a standard antibiotic used in COPD exacerbations. The NIMP will be provided to all participants at the time of randomisation by the surgery and be open-labelled. The instructions will be to take one 200mg tablet for the first day and 100mg tablet daily for the following 6 days.

8.3. Storage of IMP

The study drugs will be batched, shipped and sent to the trial management team by Tiofarma BV on behalf of WGK Ltd Pharmaceutical Manufacturing Unit. All surgeries will be randomly allocated individual batches of study drugs, via the electronic randomisation system, which will be transferred to the given surgery by a member of the research team. The study drugs held at the surgeries will be stored with temperature monitoring until dispensed by a member of the research team.

As the rate of recruitment will differ across surgeries, to allow for future resupply the remaining bulk of the drugs will be stored in the Respiratory Medicine Unit's cold room at the John Radcliffe Hospital which will be temperature monitored.

8.4. Compliance with Trial Treatment

Compliance will be assessed at the first follow-up (Day 14) visit; where the return and the quantification of the IMP will be completed. Non-compliance will be quantified if less than 5 days of the IMP were taken.

The participant is only required to take 14 tablets but will be provided with 15 tablets to allow an overage of 1 tablet should any be lost. Should a participant take all 15 tablets during the 14 days, there are no known risks associated with this as a daily dose of the active IMP can be tolerated in humans up to 60mg per day for a consecutive duration of two months. However, if this does happen, a protocol deviation form will be completed to account for the additional tablet being taken.

8.5. Accountability of the Trial Treatment

Accountability of the original shipping will be held by WGK Ltd Pharmaceutical Manufacturing Unit and a copy will be kept in the TMF. The Trial Manager will perform the initial accountability of the IMP on receipt of the shipment and will update the electronic randomisation system with the received stock. When stock is electronically randomly allocated out to surgeries by the Trial Manager, the stock will be boxed and taken by a member of the research team to the site. A member of the research team at the surgery will be responsible for logging electronic receipt of the drugs via the randomisation system once the drugs are on site.

Succeeding a randomisation, accountability of the dispensed IMP will be recorded by research personnel on an accountability log held at the GP surgeries. Any returns will be logged and disposed of as per local surgery procedure.

At the end of the trial, all unused IMP will be returned to ORTU and final drug destruction will be made.

8.6. Concomitant Medication

There are no contraindications to concomitant medication usage. Cautions and precautions summarised in the SmPC will be followed during this trial.

8.7. Post-trial Treatment

There will not be provision of the IMP beyond the trial period.

9. SAFETY REPORTING

9.1. Definitions

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.
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. 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 case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Unrelated – Where an event is not considered to be related to the IMP / intervention

Possibly Related – although a relationship to the IMP / intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably Related – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP / intervention

Definitely Related – the known effects of the IMP, its therapeutic class or based on challenge testing suggests that the IMP / intervention is the most likely cause.

9.3. Procedures for Recording Adverse Events

Only AEs leading to discontinuation of the study occurring during the treatment phase (14 days after randomisation) that are observed by the Investigator or reported by the participant, will be recorded. AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication and action taken. Follow-up information should be provided as necessary. The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant will be followed-up and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

9.4. Safety

The safety of participants will be overseen at sites by the local Principal Investigator.

9.5. Foreseeable Adverse Events

Exacerbations of COPD are associated with a risk of hospitalisation and mortality (hospitalised exacerbation mortality 10% at 1 month; 30% at 3 months and 50% at 2 years). Up to 50% of exacerbations following treatment lead to re-treatment, hospitalisation or death. These events are outcomes in the study and will therefore not be reported as adverse events or serious adverse events in this study.

9.6. Reporting Procedures for Serious Adverse Events

All SAEs (other than those defined as foreseeable above) occurring within the first 14 days of the IMP administration will be reported. All SAE information must be recorded on an ORTU SAE form and scanned and emailed to ORTU within 24 hours of the Site Study Team becoming aware of the event. ORTU will perform an initial check of the report, request any additional information and forward to an ORTU Medical Reviewer for review. The SAE will also be reviewed at the next ORTU Safety Oversight Group meeting. ORTU will oversee the tracking of SAEs in a safety tracking spreadsheet and any queries will be raised with the site team.

Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and emailed to ORTU.

9.7. Expectedness

Assessment of Expectedness will be determined by an ORTU Medical Reviewer and according to the current MHRA approved RSI section of the Summary of Product Characteristics.

9.8. SUSAR Reporting

All SUSARs will be reported by the CI (or delegate) to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the

Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days. Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial and treatment codes will be un-blinded for specific participants.

9.9. Safety Monitoring Committee

The Oxford Respiratory Trials Unit (ORTU) Safety Oversight Group (SOG) will conduct a review of all SAEs for the trial reported during the reporting period and cumulatively. The ORTU Safety Oversight Group requires at least three clinicians to attend each meeting (this may include the Chief Investigator). The Group will provide advice to the TSC and may correspond directly with the Sponsor if potential safety concerns are raised. The detailed aims and responsibilities of this committee are covered in the ORTU SOG charter and include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

The content and timings of the ORTU Safety Oversight Group will be detailed in a Safety Oversight Group Charter, which will be agreed with the members.

9.10. Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required) and Sponsor.

10. STATISTICS

Full details of the statistical analysis will be detailed in a separate statistical analysis plan (SAP) which will be drafted early in the trial and finalised prior to the primary analysis data lock. Stata (StataCorp LP) or other appropriate validated statistical software will be used for analysis. A summary of the planned statistical analysis is included here.

10.1. Description of Statistical Methods

Descriptive statistics will be used to describe the demographics between the treatment groups.

For continuous variables, the difference in the means and the corresponding 95% confidence interval will be reported for each treatment group and overall. For continuous variables, t-tests (or ANCOVA) will be applied if normally distributed to compare the intervention and control group. If not normally distributed, non-parametric techniques will be used. For categorical variables, the number (and percentage) of patients in each category will be reported for each treatment group and overall. For categorical variables, chi-squared tests will be used for comparing treatment groups if the variables are normally distributed. If a variable is not normally distributed, a non-parametric test will be used for the analysis. The primary outcome is the proportion of participants who have a treatment failure, defined as requiring retreatment, hospitalization or death. This will be analysed using the chi-squared test. The odds ratio and corresponding 95% confidence interval will be reported as well as the proportion in the two treatment arms. Secondary analysis will be undertaken using logistic regression with adjustment for the stratification and other important prognostic factors.

10.2. The Number of Participants

At 80% power and 5% significance (2-sided, the proposed sample size is 182 participants (91 per arm) providing data at 30 days in order to detect a 50% reduction in treatment failure rate from an expected rate of 40% in the control arm to 20% in the intervention arm. To allow for 20% loss to follow-up, this target is inflated to 228 participants (114 per arm).

To calculate estimated sample size literature review of previously performed randomised prednisolone placebo controlled trials (RCT's) was performed to calculate treatment failure rates in this study. There are 4 studies that have had prednisolone or placebo treatment for COPD exacerbations. In the largest of these studies Niewoehner et al [8], treatment failure occurred in 24% and 33% of the prednisolone and placebo arms respectively. In a study by Aaron et al [9], treatment failure in moderate exacerbations of COPD occurred in 27% of patients on treatment (and 43% in the placebo group). Finally, in the smallest of these RCT's study the treatment failure rate in the prednisolone and placebo group in the study by Davies et al [37], occurred in 59% and 35% respectively. In our own STARR observational study, the treatment failure rate is 50%. Using this data, the estimated treatment failure rate in the standard prednisolone treatment group is approximately 40% and the study will be powered to demonstrate that the intervention (blood-eosinophil directed treatment) will reduce this by 50%, thus treatment failure rates will be 20%. In addition to this, a 7.5% absolute difference in the rate of treatment failure has been previously specified as the clinically meaningful upper limit between the intervention groups, as previously demonstrated [8]. In other words, withholding glucocorticoids would be considered the preferred treatment if the results showed a difference in the failure rate (the rate with placebo minus the rate with active treatment) of 7.5% or less.

10.3. The Level of Statistical Significance

All tests will be completed at a 5% 2-sided significance level. All comparative outcomes will be presented as summary statistics with 95% confidence intervals and reported in accordance with the CONSORT Statement (http://www.consort-statement.org). P-values will be reported to 3 decimal places.

10.4. Criteria for the early Termination of the Trial

No anticipated early termination of the study due to IMP is expected.

10.5. Inclusion in Analysis

The modified intention to treat population will include all randomized participants who provide the primary endpoint, grouped by allocated treatment arm, irrespective of the treatment actually received. The per-patient population

includes those participants who complied with the protocol in terms of eligibility, treatment and availability of outcome measurements. Full details of the exclusions from this population will be detailed in the SAP. All analyses will be performed on an intention-to-treat basis with sensitivity analyses run on the per protocol population. Exploratory analysis for eosinophil change and mediator change will be performed. Mediators will be measured using the Meso-scale device or single enzyme-linked immunoabsorbant assay to see changes from stable to exacerbation to recovery. The mediators will include, interleukin 2,4,5,13 and tumor necrosis factor.

Procedure for Accounting for Missing, Unused, and Spurious Data

Missing data will be minimised by careful data management. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented by treatment arm. All data collected on data collection forms will be used, since only essential data items will be collected. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis.

The nature and mechanism for missing variables and outcomes will be investigated, and if appropriate multiple imputation will be used. Sensitivity analyses will be undertaken assessing the underlying missing data assumptions. Any imputation techniques will be fully described in the Statistical Analysis Plan.

Procedures for Reporting any Deviation(s) from the Original Statistical Plan

A detailed statistical analysis plan will be drawn up early in the trial with review and appropriate sign-off following OCTRU SOPs. Any changes to the statistical analysis plan during the trial will be subject to the same review and sign-off procedure with details of changes being included in the new version. Any changes/deviations from the original SAP will be described and justified in protocol and/or in the final report, as appropriate.

11. DATA MANAGEMENT

11.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. The study will have a data management plan. All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

11.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11.3. Data Recording and Record Keeping

All trial data will be captured on two-copy NCR paper CRFs. One copy will remain in the site file and the other will be held in a secure filing cabinet at the NDM. Participants' trial data will be identified only by their trial number. No identifiable details will be stored in the database or transmitted in any electronic data file.

Data will be entered from CRFs onto a secure, validated, GCP-compliant electronic data management system (OpenClinica Enterprise). All staff performing data entry will be appropriately trained prior to access being granted. Access to OpenClinica is controlled by individual user accounts, and a full audit trail is kept of all modifications made to data. The study database will be hosted on a University of Oxford server with hosting services provided by the University's Medical Sciences Division IT Unit (MSD-IT). The database will be backed up at least daily.

Standard Operating Procedures (SOPs) will be followed to ensure quality control. The processes for validation of study data will be detailed in the study monitoring plan, data management plan, and other associated documents. The Chief Investigator and/or Principal Investigator will facilitate access to study records for the purpose of monitoring, audits, and regulatory inspections. Patients' consent to this will be sought at the time of enrolment into the study. Both paper and electronic trial data will be retained through an archiving service as per the sponsoring institute's policy, and data will be retained for a minimum of 10 years after termination of the trial.

The participants will be identified by a unique trial specific number and/or code in any database. Participant identifiable details (name and telephone number) will be stored in a password protected file secure University of Oxford server, accessed only by nominated research staff, to facilitate contact with participants at the non-face-to-face follow-up visit.

12. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. CTRG & ORTU monitoring will be performed according to GCP; the frequency of which will be decided following a Risk Assessment of the Trial. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

The Trial Steering Committee, consists of both independent members as well as researchers working on the study, who will meet to provide overall supervision for the trial, concentrating on trial progress, patient safety and recruitment strategies. The TSC will meet at least annually (as per the TSC charter) and will comprise of an independent Chairperson, CI, independent statistician, GP representative, and other independent members including patient representatives.

13. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

14.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

14.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the General Data Protection Regulation (GDPR and Data Protection Act 2018), which requires data to be anonymised as soon as it is practical to do so.

14.6. Other Ethical Considerations

Participants will be enrolled into a standard arm, which will result in corticosteroids and antibiotic prescription. The blood eosinophil directed arm will receive i) corticosteroids and antibiotics or ii) placebo and antibiotics. Those prescribed placebo, and thus withholding of prednisolone are not different to usual care which is usually, prednisolone and or antibiotic therapy. Data gathered in primary care, suggest that up to 50% of patients with an exacerbation receive antibiotic therapy alone. Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

15. FINANCE AND INSURANCE

15.1. Funding

This study is funded by the National Institute of Health Research.

15.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

16. PUBLICATION POLICY

The final results of the study will be submitted for publication in peer-reviewed scientific journals for publication and dissemination. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. All data will be anonymised for publication. Public dissemination of the study results will be via patient led organisations such as the British Lung Foundation and the Breathe Easy groups. Patient and Public Involvement (PPI) will be specifically sought to address dissemination of results and compilation of update or end of study newsletters to the participants.

Contractual stipulation for the funding body is that the NIHR will be notified prior to publication (oral, written or other form) of the research data. The CI shall send one draft copy of the proposed publication to the NIHR Authority's Representative at the same time as submission for publication or at least 28 days before the date intended for publication whichever is earlier. The CI shall ensure that the outcome of the Research is prepared for publication in a suitable peer-reviewed journal and shall ensure that it, and any other publication, including patent applications, of or resulting from research carried out under this Contract shall acknowledge the Authority's financial support and carry a disclaimer as the Authority may require or in the absence of direction from the Authority a notice as follows:

"This report is independent research supported by the National Institute for Health Research (Post- Doctoral Fellowship, Dr Mona Bafadhel, PDF-2013-06-052). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health."

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18. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	20 Jul 2017	Mona Bafadhel	Section 3.5: 'Pregnant and breastfeeding women' added to exclusion criteria. Section 9.4: Removal of statement on how to treat participants in clinical condition deteriorates.
2	3.0	16 Aug 2017	Mona Bafadhel	Section 7.5: the word 'include' added Section 9.3; description of AE follow-up edited Section 10.1: minimisation changed to stratification
3	4.0	23 Jan 2018	Mona Bafadhel	Wording of primary outcome measure changed from 'frequency' to 'proportion' throughout. Modification to NIMP dosage throughout. Section 7.7: Clarification of the 12 month note review. Section 7.8: Simplification of the withdrawal procedure for this trial. Section 7.9: Modification of end of trial definition.
4	5.0	19 Aug 2018	Mona Bafadhel	Key trial Contacts: Addition of trial manager details Section 1: addition of exacerbation events Section 5: Study duration – added details of re-randomisation. Addition of exacerbation events to sample size Section 7.4: Randomisation eligibility Section 7.6.2: Patients re-randomised for additional exacerbation episodes, detail added. Section 7.6.5: Follow-up visits detail included for re-randomised visits Section 7.9: Added word 'final' Section 14.5: Additional sentence for GDPR
5	6.0	07 Mar 2019	Magda Laskawiec-Szkonter	Changes to SAE reporting process. Removal of a reference to allergic reactions upon request of the Sponsor. Removal of reference to Feno assessments as they are not being performed.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.

19. APPENDIX B:

Spirometry

The forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and slow vital capacity (SVC) will be measured at each visit using standard spirometry. Spirometry measurements will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the American Thoracic Society[36]. For FEV1 and FVC determinations, at least 3 acceptable spirometry efforts (with no more than 8) should be obtained. Acceptable spirometry efforts should have a satisfactory start of test and end of test (i.e. a plateau in the volume-time curve) and be free from artefacts due to cough, early termination, poor, obstructed mouthpiece, equipment malfunction, or other reasons. Calibration records will be kept as source documentation. At stable visits whenever possible both pre and post-bronchodilator data measurements will be recorded. At exacerbation only post-bronchodilator measurements of FEV1 and FVC will be captured.

Near patient pin-prick blood sampling

Near patient test analysis will be performed using the HemoCue WBC DIFF® and QuikRead® CRP analyser. This provides the blood differential cell count and CRP within a few minutes from a very small amount of blood (10µL, equivalent to 1 finger-prick blood spot for each test). Using a completely sterile technique, prick the lateral edge of the proximal third of the digit for sampling and sample according to the manufacturer's recommendations.

COPD Assessment Tool (CAT)

The COPD Assessment is a validated, short and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD[38]. The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, subjects rate their experience on a 6-point scale, ranging from 0 (maximum impairment) to 5 (no impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact.

Visual Analogue Scale (VAS)

The VAS is a 100 mm length line where patients will simply mark on the line how they feel from no symptom to worst ever. This will be measured using a ruler and recorded in the eCRF. VAS will be measured for dyspnoea, cough, and sputum production (volume) and sputum purulence (colour) and has been validated for use in COPD patients[32].

EuroQoL 5D (EQ-5D-5L)

The EQ-5D-5L is a standardised instrument for use as a measure of health utility. It is designed for self-completion and is cognitively simple, taking only a few minutes to complete. The EQ-5D-5L is a two-part self-assessment questionnaire. The first part consists of five items covering five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a five-point Likert scale (no problems, slight problems, moderate problems, severe problems, and extreme problems). Respondents are asked to choose one level that reflects their "own health state today" for each of the five dimensions. Respondents can be then classified into one of 243 distinct health states. The second part is a 20-cm visual analogue scale (EQ-VAS) that has endpoints labelled "best imaginable health state" and "worst imaginable health state "anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day. EQ-5D-5L health states are converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D health states from general population samples.

Modified Medical Research Council Dyspnoea Scale (mMRC)

The MRC dyspnoea scale is a simple method used to assess the severity of breathlessness[39]. Graded 0 to 4 patients are asked to choose one of 4 statements relating to the severity of breathlessness. The higher the score the worse the breathlessness.