A pilot, randomised, double-blind, placebo-controlled, cross-over study of metformin to reduce airway glucose in chronic obstructive pulmonary disease (COPD)

SHORT TRIAL TITLE

A pilot study of metformin to reduce airway glucose in COPD

FULL/LONG TITLE OF THE TRIAL

A pilot, randomised, double-blind, placebo-controlled, cross-over study of metformin to reduce airway glucose in chronic obstructive pulmonary disease (COPD)

ACRONYM

Metformin and **A**irway **G**lucose **I**n **C**OPD (**MAGIC**)

PROTOCOL VERSION NUMBER AND DATE

Version 4. 03/08/2022

RESEARCH REFERENCE NUMBERS

IRAS Number:	247421
EudraCT Number:	2018-001755-12
ISRCTN Number / Clinical trials.gov Number:	TBC
SPONSORS Number:	
FUNDERS Number:	P74536

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 publically 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: Date:
..../...../.....

Name (please print):

.....

Position:
.....

Chief Investigator:

Signature: Date:
..../...../.....

Name: (please print):

Sebastian Johnston

(Optional) Statistician:
Signature:
.....

Name: (please print):

.....

Position:
.....

KEY TRIAL CONTACTS

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Committees	N/A

i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
ICTU	Imperial Clinical Trials Unit
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation

MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAM	Synthetic Absorption Matrix
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

iii. TRIAL SUMMARY

Trial Title	A pilot, randomised, double-blind, placebo-controlled, cross-over study of metformin to reduce airway glucose in chronic obstructive pulmonary disease (COPD)	
Internal ref. no. (or short title)	A pilot study of metformin to reduce airway glucose in COPD	
Clinical Phase	Exploratory Phase II pilot study	
Trial Design	Randomised, double-blind, placebo-controlled, cross-over	
Trial Participants	Chronic obstructive pulmonary disease (COPD) patients	
Planned Sample Size	40 subjects	
Treatment duration	3 months one study arm, 2 weeks wash out, 3 months in other study arm	
Follow up duration	6.5 months	
Planned Trial Period	24 months	
	Objectives	Outcome Measures
Primary	Effect of metformin on airway glucose	Sputum glucose after 3 months treatment with metformin
Secondary	Effects of metformin on: 1. Glucose levels in the nose 2. Bacterial infection 3. Inflammation in the lung 4. COPD exacerbations 5. Quality of life and symptoms 6. Lung function	1. Glucose levels in nasal SAM strips 2. Bacterial load in sputum 3. Inflammatory markers in sputum 4. Number of COPD exacerbations 5. Quality of life and symptom scores 6. Spirometry
Investigational Medicinal Product(s)	Metformin	
Formulation, Dose, Route of Administration	1000mg bd, po	

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
NIHR Imperial Biomedical Research Centre (BRC)	£ 173,511

v. ROLE OF TRIAL SPONSOR AND FUNDER

Imperial College is the Trial Sponsor responsible for the initiation and management of the trial. The funder had no input into the trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results

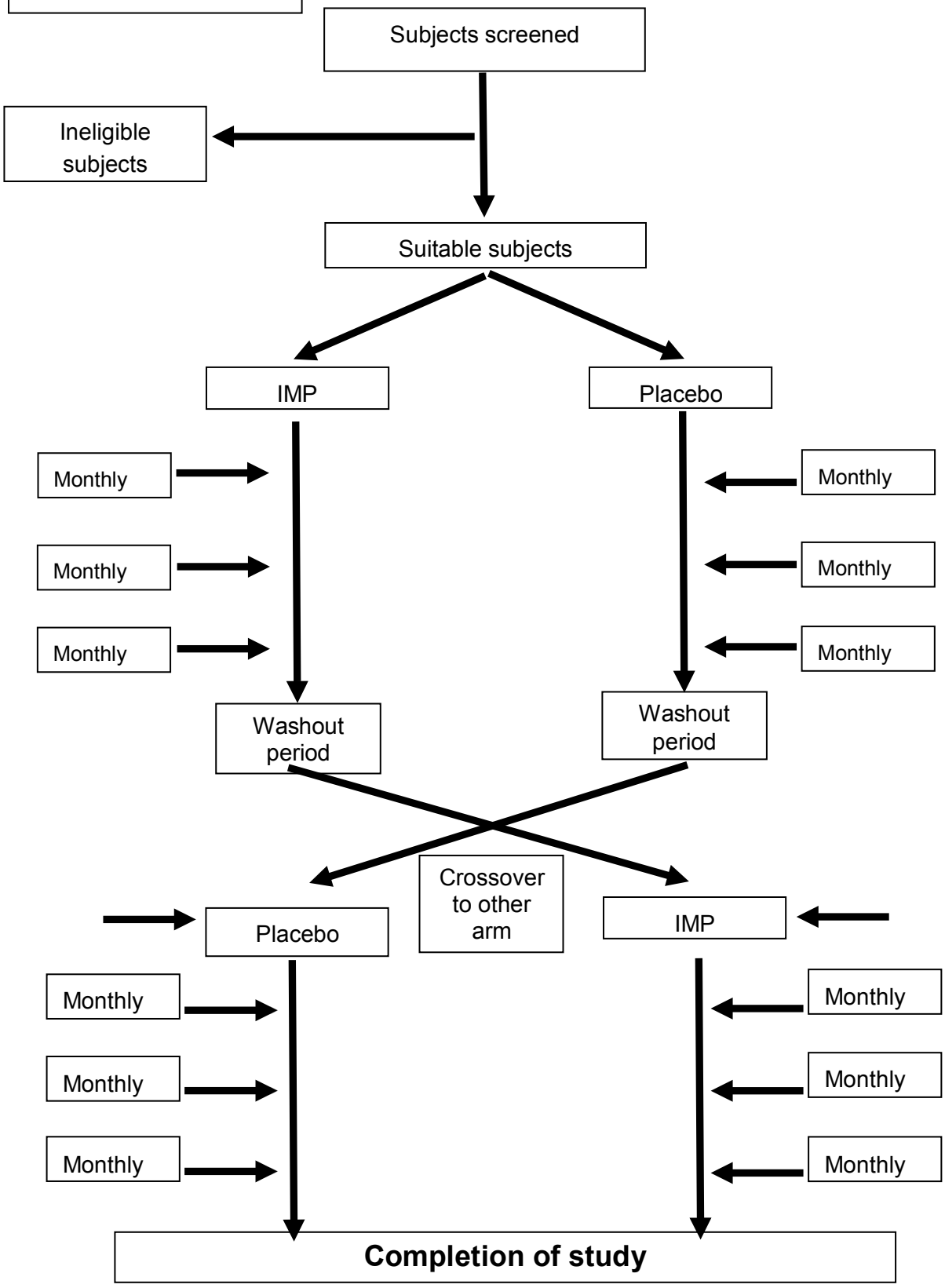
vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

vii. Protocol contributors

The protocol was written by Dr Patrick Mallia, Dr J Tregoning and Professor Sebastian Johnston.

viii. KEY WORDS: COPD, lung glucose, metformin, pilot study, cross-over trial

ix. TRIAL FLOW CHART



1 BACKGROUND

Chronic obstructive pulmonary disease (COPD) is the 4th leading cause of death worldwide and continues to increase in prevalence (1). Lung infection plays a major role in disease progression and acute exacerbations. Bacterial infection is detected in 30-40% of stable COPD patients and is associated with disease progression, airway inflammation, impaired quality of life, more symptoms and frequent exacerbations (2). COPD patients frequently experience acute exacerbations that are associated with enormous morbidity, mortality and frequent hospitalisation, and bacteria are detected in 50-60% of exacerbations (2). Use of antibiotics to treat COPD exacerbations contributes to the development of antibiotic resistance. Therefore there is a clear unmet medical need to develop antibiotic-independent approaches to reduce bacterial infection in COPD. This has the potential to improve outcomes in COPD and reduce exacerbations. Glucose concentrations in the lungs are increased in COPD patients and linked to bacterial infection (3). This suggests that reducing airway glucose may be a promising potential therapeutic strategy

2 RATIONALE

COPD affects 1.2 million people in the UK, costing the NHS >£800 million annually. COPD patients are more susceptible to both chronic and acute bacterial infections. Patients with chronic lung bacterial infection have worse quality of life, faster disease progression, more symptoms and frequent exacerbations. Acute respiratory infections are the main cause of acute COPD exacerbations which cause COPD patients to become acutely unwell and often result in hospitalisation, especially in the winter. Bacteria are detected in 50-60% of COPD exacerbations. Antibiotics are frequently used to treat COPD exacerbations and this contributes to the development of antibiotic resistance. Therefore any intervention that prevents or reduces bacterial infection in COPD, especially if it is not an antibiotic, will have major benefits for COPD patients, the NHS and for society as a whole.

It is likely that there are many reasons why COPD patients are more susceptible to bacterial infections. From experimental work we have carried out we believe that one of the reasons is high glucose concentrations in the lung (3). In healthy lungs glucose levels are kept low and this is probably to inhibit bacterial growth by depriving them of an essential nutrient. In animal studies if levels of glucose in the lung are high, bacterial lung infection is more common (4). We measured lung glucose concentrations in COPD patients and found that they are higher compared with people without COPD.

COPD patients with higher levels of glucose also had more bacteria in their lungs and sputum samples from COPD patients with higher glucose concentrations supported greater bacterial growth (3).

Therefore this study was the first to link elevated glucose in the lung to bacterial infection in COPD. Therefore reducing airway glucose has the potential to inhibit bacterial growth in COPD patients. One potential approach is to use the anti-diabetic drug metformin. In animal studies we have demonstrated that metformin decreases airway glucose and bacterial colonisation (4). The aim of the proposed study is to investigate whether metformin can achieve the same effects in COPD patients. Metformin is safe, cheap, does not cause hypoglycaemia and has been extensively used in COPD patients with diabetes with an excellent safety record (5). The primary aim of this study will be to evaluate the effects of metformin on lung glucose in COPD patients. If the study successfully demonstrates that metformin reduces airway glucose it will provide the data needed to justify a clinical trial of metformin with exacerbations as the primary outcome.

2.1 Assessment and management of risk

Risks related to metformin

The side effects of metformin are mainly gastrointestinal. The relevant summary of product characteristics (SmPC) lists gastrointestinal disorders, such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, as very common (frequency >1/10). It states that these side effects 'occur most frequently during initiation of therapy and resolve spontaneously in most cases.' Taste disturbance is listed as a common side effect (frequency >1/100). All other side effects are described as very rare (<1/10,000) or not known (cannot be estimated from available data). In accordance with the SmPC, to minimise gastrointestinal effects as far as possible, the study tablets will be administered after meals, and the dose will be escalated gradually to the target dose.

Hypoglycaemia:

Metformin does not induce low blood sugar levels (hypoglycaemia) when used as the sole glucose-lowering therapy in diabetic patients. It does not exert a hypoglycaemic action in non-diabetic patients unless taken in overdose. Even in the setting of overdose, hypoglycaemia has not been seen with metformin doses up to 85g. As diabetes is an exclusion criterion, the use of other oral glucose-lowering agents will not be permitted in this study.

Although not listed in the SmPC, it is suggested that there may be a risk of hypoglycaemia if metformin is administered in the setting of malnutrition, inadequate caloric intake, or excessive alcohol consumption. Therefore these will be exclusion criteria in this study.

Lactic acidosis:

A predecessor of metformin - phenformin - has been associated with lactic acidosis. However a systematic review published in 2010 evaluated the risk for lactic acidosis in type 2 diabetic patients taking metformin and showed no cases of fatal or nonfatal lactic acidosis in 347 prospective trials and cohort studies with more than 70,490 patient-years of metformin use. The authors concluded that there is no evidence that metformin is associated with an increased risk of lactic acidosis (6).

Metformin and COPD

Metformin is routinely used in COPD patients who also have diabetes. There are 3 studies of metformin use in COPD patients and serious adverse effects were not reported. In fact these studies found that COPD patients taking metformin had less breathlessness, less exacerbations, less hospitalisations and longer survival (5, 7, 8). A systematic review and meta-analysis of the adverse effects of metformin in polycystic ovarian disease (PCOS) also found that metformin was safe and well-tolerated (9). Therefore from the available studies metformin has been reported safe in COPD (and may actually have beneficial effects) and in non-diabetic patients with PCOS.

Risks related to study procedures

Sputum induction carries a small risk of bronchoconstriction. We have performed sputum inductions in COPD patients for >15 years and we have a well-established protocol to minimise the risk of bronchoconstriction and detect immediately if it occurs. Using this protocol we have carried out >350 inductions with no adverse events, including in patients with severe COPD and in COPD patients during acute exacerbations

This trial is categorised as:

• Type B (somewhat higher than the risk of standard medical care). As the study participants will be taking and additional medication to their usual medical care there is an increased risk of adverse effects. However as the medication is licensed and has been extensively used in this population group with minimal adverse effects (and possibly beneficial effects – see references 5, 7 and 8) this study is not Type C (Markedly higher the risk of standard medical care).

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

To determine the effect of metformin on the glucose in sputum in COPD patients after 3 months treatment with metformin.

3.2 Secondary objectives

Secondary objectives will be to determine the effect of metformin on:

1) Nasal glucose
2) Bacterial infection
3) Inflammatory markers in sputum
4) COPD exacerbations
5) Quality of life and symptoms
6) Lung function

3.3 Outcome measures/endpoints

3.4 Primary endpoint/outcome

The median concentration of glucose in sputum in COPD patients after 3 months treatment with metformin compared with 3 months of placebo.

3.5 Secondary endpoints/outcomes

These will also be assessed in COPD patients after 3 months treatment with metformin compared with placebo.

1) Median glucose concentration measured in nasal SAM strips
2) Bacterial infection (sputum semi-quantitative culture)
3) Inflammatory markers measured in sputum
4) Number of COPD exacerbations
5) Quality of life/symptom scores
6) Lung function measured using spirometry

3.6 Exploratory endpoints/outcomes

Nil

3.7 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To determine the effect of metformin on sputum glucose in COPD patients	The median concentration of glucose in sputum in COPD patients after 3 months treatment with metformin compared with placebo.	3 months
Secondary Objectives To determine the effect of metformin on: 1) Nasal glucose 2) Bacterial infection 3) Inflammatory markers in sputum 4) COPD exacerbations 5) Quality of life and symptoms 6) Lung function	1) Median glucose concentration measured in nasal SAM strips 2) Bacterial infection (sputum semi-quantitative culture) 3) Inflammatory markers measured in sputum 4) Number of COPD exacerbations 5) Quality of life/symptom scores 6) Lung function measured using spirometry	3 months

4 TRIAL DESIGN

The proposed study will be a randomised, double-blinded, placebo-controlled, cross-over study of metformin in patients between the ages of 40 and 75 with a confirmed diagnosis of COPD. It will be an exploratory pilot trial, to gather preliminary information on the effects of metformin on sputum glucose and the feasibility of conducting a full-scale trial.

All subjects will have clinical assessments and blood, airway samples (nasal SAM and sputum) collected at baseline prior to the treatment phase. Clinical assessments will include lung function (FEV_1 and FVC), quality of life and symptom questionnaires (St George's Respiratory Questionnaire, COPD assessment test). Subjects will then either be commenced on metformin or placebo for a period of 3 months and blood, sputum and nasal samples collected at monthly intervals. Following a 2 week washout period the subjects will crossover to the other study arm for another 3 months and repeat samples collected.

Primary Outcome

The primary outcome will be sputum glucose measured using an enzymatic assay (AmplexRed® – ThermoFisher) after 3 months treatment with metformin. There is currently no data on which to base a power calculation and therefore this pilot study will assess what the size of any effect of metformin is in COPD subjects and thereby provide data that can be used to power any future, larger clinical trials.

5 TRIAL SETTING

Imperial College Healthcare NHS Trust, St Mary's Hospital, London and Imperial College London

6 PARTICIPANT ELIGIBILITY CRITERIA

The trial population will be patients with a diagnosis of COPD who fulfil the inclusion/exclusion criteria outlined below

6.1 Inclusion criteria

Age 40-85 years

A clinical diagnosis of COPD confirmed with spirometry (Post-bronchodilator FEV_1/FVC <70%)

A smoking history of at least 15 pack years

Absence of infection for at least 8 weeks prior to study entry

No use of antibiotics and oral corticosteroids at least 8 weeks prior to study entry

Able to understand and consent to the study procedures

6.2 Exclusion criteria

Diagnosis of diabetes irrespective of treatment

Diabetes diagnosed on screening bloods

History of hepatic/renal impairment or hepatic/renal impairment diagnosed on screening bloods

Excessive alcohol intake (>21 units/week in males and >14 units in females)

BMI < 18.5kg/m2

Taking metformin irrespective of indication

History of allergy or hypersensitivity to metformin or hypersensitivity or intolerance to any of the placebo compounds

Pregnancy or breastfeeding

Unable to provide informed consent

Any contraindication for Metformin treatment as detailed in Metformin SmPC including:

Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock

Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock

Any type of acute metabolic acidosis

7 TRIAL PROCEDURES

All subjects will have clinical assessments and blood, airway samples (nasal SAM and sputum) collected at baseline prior to the treatment phase. Clinical assessments will include lung function (FEV_1 and FVC), quality of life and symptom questionnaires (St George's Respiratory Questionnaire, COPD assessment test). Women of childbearing potential will only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test. Subjects will then either be commenced on metformin or placebo for a period of 3 months and blood, sputum and nasal samples collected at monthly intervals. Following a 2 week washout period the subjects will crossover to the other study arm for another 3 months and repeat samples collected.

7.1 Recruitment

The study will be carried out in conjunction with the clinical team at Imperial College Healthcare NHS Trust. The PI is part of this team. Potential participants will be identified from COPD patients attending the clinical service. The applicant will identify potential participants.

7.1.1 Participant identification

Potential participants will be identified from COPD patients attending the clinical service. The PI who is part of the normal clinical team will identify potential participants and confirm eligibility.

7.1.2 Screening

A clinical diagnosis of COPD

7.1.3 Payment

A payment of £50 plus travel expense will be offered as compensation for the participants' time.

7.2 Consent

The PI will obtain informed consent from all participants. Potential participants will be provided with written information if they express an interest in participating in the study and given time to read this and discuss any questions that arise from this prior to providing informed consent. We will not recruit participants who have difficulties in adequately understanding written or verbal information in English.

7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Samples collected during the course of the study will be used for pre-specified analyses and any unused samples will be stored in an ethically approved research tissue bank for future specified or unspecified research. Participants will be asked for consent for use in future research related to the clinical condition under trial and may opt out but still participate in the main trial.

7.3 The randomisation scheme

Simple randomisation

7.3.1 Method of implementing the randomisation/allocation sequence

The randomisation will be carried out using INFORM.

7.4

Blinding

The trial participants, care providers and outcome assessors will all be blinded. Randomisation will be the responsibility of the trial statistician and the medication will be dispensed in a blinded fashion from the hospital pharmacy. The trial medication will be over encapsulated. The final unblinding of all trial participants will occur at the end of the study after a close out visit and the creation of a locked analysis data set.

7.5 Emergency Unblinding

The trial code will only be broken for valid medical or safety reasons e.g. in the case of a serious adverse event where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. This will be will be carried out using INFORM.

7.6 Baseline data

Baseline data collected will include:

1) Demographic data
2) Blood tests (full blood count, blood glucose, renal function, liver function tests)
3) Lung function
4) Sputum samples (either spontaneous or induced)
5) Nasal SAM strips
6) Quality of life/symptom scores

7.7 Trial assessments

After baseline assessment, participants will either be commenced on metformin or placebo for 3 months during which time the participants will have monthly visits. At these visits the following assessments will be carried out:

1) Collection of data regarding exacerbations and adverse events
2) Physical examination
3) Blood tests (renal function, liver function tests)
4) Lung function
5) Sputum samples collected (either spontaneous or induced)
6) Nasal SAM strips
7) Quality of life/symptom scores

Following a 2 week washout period the subjects will crossover to the other study arm for another 3 months and follow the same study protocol.

7.8 Long term follow-up assessments

N/A

7.9 Qualitative assessments

N/A

7.10 Withdrawal criteria

Participants will be withdrawn from the trial if:

1) They no longer wish to continue in the study and withdraw consent
2) They experience a serious adverse event
3) They experience an adverse event not related to the study medication that requires them to be withdrawn (e.g. they develop renal or hepatic impairment).

7.11 Storage and analysis of clinical samples

The samples will all be processed and stored in the laboratories in the Department of Respiratory Medicine at Imperial College, St Mary's campus according to previously established laboratory protocols.

7.12 End of trial

The end of the trial will be the date of the last visit of the last patient undergoing the trial.

8 TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product(s)

The IMP is metformin. The IMP and placebo will be provided by Sharp Clinical Services Ltd (MHRA authorisation number 10284). Metformin and placebo will be packaged in an identical manner. A unique pack ID will be used to identify each pack and its content.

8.2 Regulatory status of the drug

The IMP has a MA in the UK. Repackaging and trial labelling for the trial will be carried out by Sharp Clinical Services Ltd (MHRA authorisation number 10284).

8.3 Product Characteristics

The SmPC for metformin will be provided.

8.4 Drug storage and supply

The IMP will be provided by the supplier (Sharp Clinical Services Ltd) and will be stored at and dispensed from the inpatient pharmacy at St Mary's Hospital. Each subject will be dispensed 1 month's supply when they attend for their baseline visit according to their randomisation code on INFORM. They will then be dispensed 1 month's supply at each of their follow-up monthly visits. Any remaining medication at the end of the study will be collected and counted at the pharmacy who will also be responsible for its destruction.

8.5 Preparation and labelling of Investigational Medicinal Product

The IMP will be prepared and labelled by the supplier. It will be packaged in containers each with 1 month's supply of medication.

8.6 Dosage schedules

The IMP will be commenced at a dose of 500mg twice daily. After 1 week it will be increased to 1000mg twice daily.

8.7 Dosage modifications

N/A

8.8 Known drug reactions and interaction with other therapies

Concomitant use not recommended:

Alcohol. Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment. Therefore any potential participants with excessive alcohol intake (>21 units/week in males and >14 units in females) will not be recruited.

Iodinated contrast agents. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours, provided that renal function has been re-evaluated and found to be stable.

8.9 Concomitant medication

Combinations requiring precautions for use:

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclooxygenase (COX) II inhibitors, ACE inhibitors, angiotension II receptor antagonists and diuretics, especially loop diuretics.

Organic cation transporters (OCTs) are active transporters of metformin into the hepatocyte. Drugs that inhibit or induce OCTs have the potential to interfere with the transport of metformin and affect both plasma and intracellular concentrations of metformin. However only a small number of clinically relevant DDIs with metformin have been reported including cimetidine, dolutegravir, pyrimethamine, rifampicin, trimethoprim and verapamil.

If any such products are started during the study, close monitoring of renal function will be carried out.

8.10 Trial restrictions

Women of childbearing potential (WOCBP) are defined according to the Clinical Trial Facilitation Group document (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/ Working_Groups /CTFG/2014_09_HMA_CTFG_Contraception.pdf).

A woman is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

WOCPB are required to use adequate contraception for the duration of the trial. This includes:

1) Intrauterine Device (IUD)
2) Hormonal based contraception (pill, contraceptive injection etc.)

3) Double Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
4) True abstinence. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

8.11 Assessment of compliance with treatment

Subjects will complete a diary card recording medication usage and return any unused medication that will be counted at the monthly visits. Percentage of noncompliance acceptable for a subject to continue in the trial is <80%.

8.12 Name and description of each Non-Investigational Medicinal Product (NIMP)

N/A

9 PHARMACOVIGILANCE

9.1 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 IMP which is related to any dose administered to that participant. The phrase "response to an IMP" 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 the time of the event or any valid alternative etiology 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 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:

9.2 Operational definitions for (S)AEs

As the IMP has a well-known and well established safety profile, new or unreported AEs and ARs are not expected in such a small trial. All AEs and ARs will be recorded. Acute exacerbations are expected to occur in COPD patients and therefore will not be recorded as (S)AEs or ((S)ARs). Breaking the blind will only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical management of the participant

9.3 Recording and reporting of SAEs, SARs AND SUSARs

All SAEs / SAEs occurring from the time of written informed consent until 30 days post cessation of trial treatment must be recorded on the AE Form and emailed to the Sponsor (JRCO.CTIMP.TEAM@imperial.ac.uk) within 24 hours of the research staff becoming aware of the event.

For each SAEs the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- Whether the event would be considered anticipated.

Any change of condition or other follow-up information should be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All ARs/SARs/SUSARs occurring from the time of start of trial treatment until 30 days post cessation of trial treatment must be recorded on the AE Form and emailed to the Sponsor within 24 hours of the research staff becoming aware of the event.

For each AR/SAR/SUSAR the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- Whether the event would be considered anticipated.

Any change of condition or other follow-up information will be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The CI/delegated team will inform the Sponsor, MHRA, the REC and Marketing Authorisation Holder (if not the sponsor) of SUSARs within the required expedited reporting timescales: fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

9.4 Responsibilities

Chief Investigator (CI):

1. Checking for AEs and ARs when participants attend for treatment / follow-up.
2. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
3. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
4. Using medical judgement in assigning whether and event/reaction was anticipated or expectedness in line with the Reference Safety Information.
5. Immediate review of all SUSARs.
6. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

7. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
8. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
9. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.
10. Expedited reporting of SUSARs to the MHRA and REC within required timelines.
11. Notifying Investigators of SUSARs that occur within the trial.
12. Checking for and notifying PIs of updates to the Reference Safety Information for the trial.

Sponsor:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. The unblinding of a participant for the purpose of expedited SUSAR reporting.

9.5 Notification of deaths

All deaths, including deaths deemed unrelated to the IMP, if they occur earlier than expected will be reported to the sponsor".

9.6 Pregnancy reporting

All pregnancies within the trial (either the trial participant or the participant's partner, with participants consent) should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification

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 serious criteria, this would be considered an SAE

9.7 Overdose

An overdose will be defined as taking more than the study dose of medication as reported by the patient or from pill counts. It will be recorded as an AE or SAE. The CI will decide whether the patient will be withdrawn from the trial

9.8 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

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

Any SUSAR will be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred until resolved.

9.10 Development safety update reports

'Reference Safety Information' in this study is section 4.8 of Metformin SmPC. The CI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or as necessary, to the Competent Authority (MHRA in the UK), where relevant the Research Ethics Committee and the sponsor. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The primary outcome will be change in sputum glucose from baseline after treatment with metformin, measured using an enzymatic assay (AmplexRed®). The median glucose concentration in COPD subjects measured in our previous study was 1,007 µM (SD 733µM). Metformin reduced airway glucose by c.30% in studies carried out in mice. Therefore to detect a similar effect in humans would require 30 subjects with 90% power at 5% significance. We aim to recruit 40 subjects to account for possible withdrawals.

10.2 Planned recruitment rate

The target number of participants will be 40 that will be recruited over 12 months, therefore our target recruitment rate will be 3 – 4 participants per month.

10.3 Statistical analysis plan

10.3.1 Summary of baseline data and flow of patients

The variables to be used to assess baseline comparability of the randomised groups will include:

1) Age
2) Sex
3) Lung function
4) Number of exacerbations in the previous year
5) GOLD COPD category

A consort flow diagram will be produced

10.3.2 Primary outcome analysis

The primary endpoint (median sputum glucose in treated versus non-treated participants) will be analysed using a Mann-Whitney test. The post-treatment sputum glucose will also be compared with baseline glucose using Wilcoxon matched-pairs test. Similar methods will be used to analyse the secondary endpoints.

10.3.3 Secondary outcome analysis

Same as for primary outcome

10.7 Participant population

The participant populations whose data will be subjected to the trial analysis will be the protocol-compliant population: Any participant who was randomised and received the protocol required trial drug exposure and required protocol processing

10.8 Procedure(s) to account for missing or spurious data

As the study is a small single-centre pilot study with a single primary outcome measure we do not expect missing or spurious data.

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

All patient data will be kept on a paper CRF and electronic CRF.

11.2 Data handling and record keeping

CRFs will be kept in a dedicated facility in ICCRU. Each participant will be assigned a unique participant identification code that allows identification of all the data reported for each participant.

11.3 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 in line with participant consent.

11.4 Archiving

Archiving will be authorised by the Sponsor following submission of the end of trial report. All essential documents will be archived for a minimum of 10 years after completion of trial and destruction of essential documents will require authorisation from the Sponsor.

12 MONITORING, AUDIT & INSPECTION

The JRCO via an assigned monitor will establish a monitoring plan which will take in consideration a risk-based approach to determine the monitoring schedule required.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will notify the REC of the end of the trial and if the trial is ended prematurely, the CI will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC and the EU trials register.

13.2 Peer review

The trial was peer reviewed by the funder (Imperial BRC)

13.4 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and Favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments. The CI will ensure that appropriate approvals from participating organisations are in place.

13.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol will not be allowed. Accidental protocol deviations will be adequately documented on the relevant forms and reported to the CI and Sponsor immediately.

13.6 Notification of Serious Breaches to GCP and/or the protocol

The sponsor will be notified immediately of any case where a serious breach occurs during the trial conduct phase. The sponsor will notify the licensing authority in writing of any serious breach of:
The conditions and principles of GCP in connection with the trial; or
The protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

13.7 Data protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of the UK Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.
Personal information collected will be kept in a secure location in a dedicated facility in ICCRU as stated previously.
Each participant will have a unique, coded, depersonalised identification number.
All clinical samples will be identified with this number.

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

The investigators have no competing interests that might influence trial design, conduct or reporting.

13.9 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

13.10 Amendments

If we wish to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, we will submit a valid notice of amendment to the licencing authority (MHRA) for consideration. If we wish to make a substantial amendment to the REC application or the supporting documents, we will submit a valid notice of amendment to the REC for consideration. Amendments also need to be notified to the R&D office

13.11 Post trial care

On completion of the trial participants will revert to their usual standard of care that currently does not include metformin.

13.12 Access to the final trial dataset

The CI will have access to the final dataset.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

On completion of the trial, the data will be analysed and tabulated and a Final Trial Report prepared. The participating investigators will have rights to publish the trial data and the funding body will be acknowledged within the publications. Participants will be notified of the outcome of the trial, if they have requested this.

14.2 Authorship eligibility guidelines and any intended use of professional writers

The investigators will be named as authors. No professional medical writers will be used.

15 REFERENCES

(1) Ferkol T, Schraufnagel D. The global burden of respiratory disease. Ann Am Thorac Soc. 2014 Mar;11(3):404-6

(2) Beasley V et al. Lung microbiology and exacerbations in COPD. International Journal of COPD 2012; 7: 555-569

(3) Mallia P et al. 2017. Role of airway glucose in bacterial infections in Chronic Obstructive Pulmonary Disease. Journal of Allergy and Clinical Immunology 2018 Sep;142(3):815-823.e6

(4) Garnett JP, Baker EH, Naik S, Lindsay JA, Knight GM, Gill S, Tregoning JS, Baines DL. 2013. Metformin reduces airway glucose permeability and hyperglycaemia-induced Staphylococcus aureus load independently of effects on blood glucose. Thorax 68:835-845.

(5) Hitchings AW et al. Safety of metformin in patients with COPD and type 2 diabetes mellitus. COPD. 2015;12(2):126-31

(6) Salpeter SR et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Systematic Rev. 2010:CD002967.

(7) Bishwakarma R et al. Metformin use and health care utilization in patients with coexisting COPD and diabetes mellitus. Int J COPD. 2018;13:793-800.

(8) Sexton P et al. Respiratory effects of insulin sensitisation with metformin: a prospective observational study. COPD. 2014;11(2):133–142

(9) Domecq JP et al. Adverse effects of the common treatments for polycystic ovary syndrome: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2013 Dec;98(12):4646-54.

16. APPENDICIES

16.1 Appendix 1- Risk

Risks associated with trial interventions
☐ A ≡ Comparable to the risk of standard medical care ☒ B ≡ Somewhat higher than the risk of standard medical care ☐ C ≡ Markedly higher than the risk of standard medical care
Metformin is a licensed medication that has been used extensively for many decades with a well described side effect and safety profile. Therefore in this study that is small, short-term and in which people at a higher risk of adverse effects will be excluded, no new, unexpected adverse effects are expected. Therefore category B is justified.

16.4 Appendix 2 – Schedule of Procedures

Procedures	Visits								
	Screening	Baseline	Treatment Phase						
			Arm 1			Arm 2			
			1 month	2 months	3 months	Baseline	1 month	2 months	3 months
Informed consent	x								
Demographics	x								
Medical history	x								
Physical examination	x	x	x	x	x	x	x	x	x
Vital signs	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x
ECG	x								
Laboratory tests	x	x	x	x	x	x	x	x	x
Eligibility assessment	x								
Randomisation		x							
Dispensing of trial drugs		x	x	x		x	x	x	
Compliance		x	x	x	x	x	x	x	x
Blood test		x	x	x	x	x	x	x	x
Sputum sample		x	x	x	x	x	x	x	x
Nasal SAM		x	x	x	x	x	x	x	x
Lung function		x	x	x	x	x	x	x	x
SGRQ		x	x	x	x	x	x	x	x
CAT		x	x	x	x			x	x
Adverse event assessments			x	x	x			x	x

16.6 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

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