CLINICAL TRIAL PROTOCOL

Trial Title:	**Optimising azithromycin prevention treatment in COPD to reduce exacerbations (OPACE): A double blind adaptive design pragmatic phase IV randomised controlled trial**
Protocol Number:	CCTU0333
CT.Gov Number:	Pending
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1 Protocol Signatures:

I give my approval for the attached protocol entitled "**Optimising azithromycin prevention treatment in COPD to reduce exacerbations (OPACE): A double blind adaptive design pragmatic phase IV randomised controlled trial"** dated.....

Chief Investigator

Name: _____

Signature: _____

Date: _____

Site signatures

I have read the attached protocol entitled "**Optimising azithromycin prevention treatment in COPD to reduce exacerbations (OPACE): A double blind adaptive design pragmatic phase IV randomised controlled trial**" dated ..... and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles Articles 2 to 5 of the Good Clinical Practice as outlined in the European Clinical Trials Directives 2005/28/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any subsequent amendments of the clinical trial regulations, The Sponsor's 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

Principal Investigator

Name: _____

Signature: _____

Date: _____

2 Protocol Contributors

Protocol contributors

The contact details for the Sponsors, Chief Investigator(s) and trial staff involved in trial management, monitoring and analysis, oversight committee members and participating centres are detailed in documents supplementary to the protocol.

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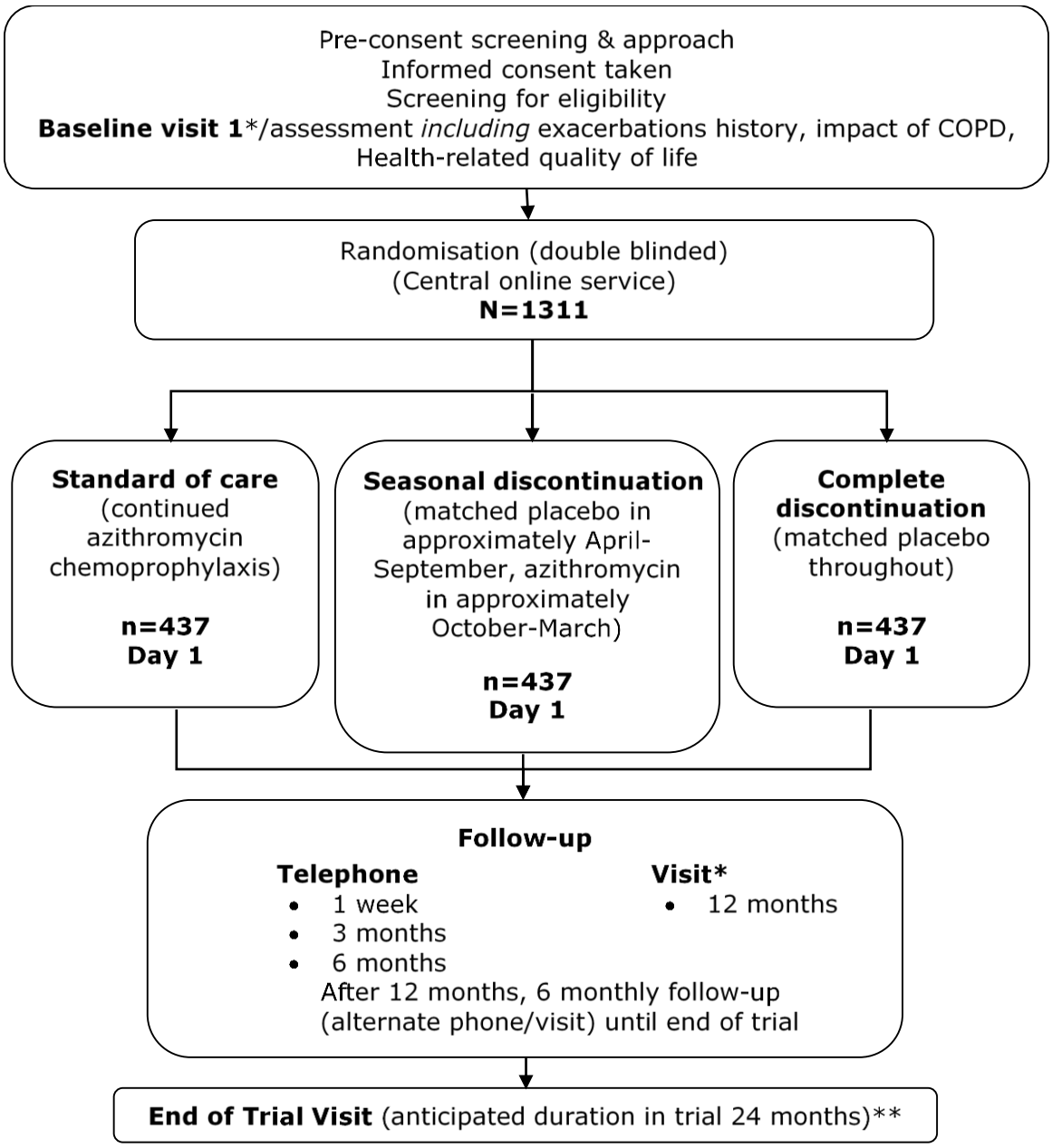
3 ABBREVIATIONS

AE/AR	Adverse event/Adverse Reaction
AESI	Adverse event of special interest
AMR	Antimicrobial resistance
BMI	Body Mass Index
BTS	British Thoracic Society
CA	Competent Authority
CCTU	Cambridge Clinical Trials Unit
CFS	Clinical Frailty Scale
CI	Chief Investigator
CI	Confidence Interval
CMMS	Cambridge Multimorbidity Score
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computerised Tomography
CTIMP	Clinical Trial of Investigational Medicinal Product
DSUR	Development Safety Update Report
eFI	Electronic Frailty Index
EQ-5D-5L	EuroQoL 5 dimensions, 5 level questionnaire
FBC	Full Blood Count
FEV_1	Forced Expiratory Lung Volume in 1 second
FPFV	First Patient First Visit
FVC	Forced Vital Capacity
GAD-2	Generalised Anxiety Disorder-2
GP	General Practitioner
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HEAP	Health Economic Analysis Plan
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
iDMC	Independent Data Monitoring Committee
IDMEC	Independent Data Monitoring and Ethics Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LPLV	Last Patient Last Visit
MACE	Major adverse cardiovascular events
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Clinical Excellence
NIHR	National Institute of Health and Care Research
PI	Principal Investigator
P-gp	P-glycoprotein
PHQ-2	Patient health questionnaire-2
PIS	Participant Information Sheet
QALYs	Quality-Adjusted Life Years
R&D	Research and Development
RA	Regulatory Agency
REC	Research Ethics Committee
SAE/SAR	Serious Adverse Event/Serious Adverse Reaction
SE	Sealed Envelope
SHS	Self-rated health status
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TPM	Trial Procedures Manual
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

4 TRIAL FLOW CHART



Key trial outcomes collected over the course of follow-up

- **Time to first COPD exacerbation-PRIMARY ENDPOINT**
- Number/rate and severity of exacerbations
- Impact of COPD (CAT score)
- Quality of life (EQ-5D-5L)
- Adverse events
- Adherence
- Hospital admissions data and mortality data *if available*, from NHS Digital/devolved administrations equivalent

* Ideally in person/dependent on participant preference and pandemic impact

** Duration in trial may be shorter or longer depending when recruited and how long trial runs for as advised by Trial Steering Committee

5 INTRODUCTION

5.1 Background

Azithromycin chemoprophylaxis to reduce the risk of COPD exacerbations in patients at high risk of exacerbations is recommended by the National Institute for Clinical Excellence (NICE), British Thoracic Society (BTS) and Global Obstructive Lung Disease (GOLD) guidelines based on Cochrane reviews of available evidence.[1-3] Clinical trials show azithromycin chemoprophylaxis markedly reduces exacerbations with possible benefit in patient reported quality of life outcomes.[4,5] However, the Cochrane review found no significant effect on COPD hospital admissions (severe exacerbations), change in lung function (Forced Expiratory Lung Volume in 1 second (FEV_1)), or mortality.[5] More recently, the BACE trial reported fewer COPD hospital admissions during 3-months of azithromycin chemoprophylaxis vs placebo, commenced at the time of a severe exacerbation.[6]

There is, however, a lack of evidence regarding both the long-term (≥12 months) efficacy of azithromycin chemoprophylaxis and benefits vs risks balance of discontinuing or continuing azithromycin prophylactic treatment in patients with COPD, at high risk of exacerbations, who have stabilised. An observational study reported on azithromycin withdrawal in 15 patients (out of 39), but azithromycin was reintroduced due to recurrence of exacerbations in nine patients; the median period without therapy was 7 months.[7] A trial in 89 patients with primary antibody deficiency and pulmonary disease showed 24 months of azithromycin reduced exacerbations and hospitalisations.[8] In contrast, retrospective analysis of 14 individuals in the COLUMBUS trial who received 24 months azithromycin treatment in total, showed no benefit of treatment beyond one year.[9] These studies are of limited value – tiny sample size, retrospective or observational.

From a risk perspective, azithromycin is a key target of stewardship programs and is a World Health Organisation (WHO) Watch group antibiotic.[10] Long-term use individually and at scale does increase antimicrobial resistance (AMR) for the individual and wider community respectively.[11,12] Use of azithromycin is associated with increased risk of cardiovascular death as evidenced from pharmacoepidemiology studies.[13,14] Given that people with COPD have increased cardiovascular risk,[15] there is need for long-term follow-up for COPD patients on treatment. Azithromycin can also cause hearing loss.[4] People with COPD often have multimorbidity, frailty and polypharmacy[16-18] and the risk of further isolating people due to difficulties in communication caused by prescribed medicines needs urgent evaluation. Multimorbidity may also impact relative benefits gained vs risks of chemoprophylaxis as suggested by NICE.[19] A further concern with long-term azithromycin treatment is potential impact on non-tuberculous mycobacteria (NTM) resistance.[20,21] This is important as azithromycin is a valuable antibiotic used in the treatment of NTM.

5.1.1 Seasonality of COPD exacerbations

COPD exacerbations display strong seasonality in temperate climates such as the UK, as evidenced by primary care usage, hospitalisations, mortality data and seasonal bed pressures.[22-28] In today's clinical practice, whether a shorter seasonal course of azithromycin is comparable, in clinical effectiveness, to long-term chemoprophylaxis is unknown, although seasonal use of azithromycin is recommended as a de-escalation approach from continued use in some local trust guidelines.[29] A historic trial of seasonal tetracyclines chemoprophylaxis vs placebo in chronic bronchitis, showed significant reduction in exacerbations in susceptible patients (those with >1 exacerbation/winter).[30] There are no seasonal chemoprophylaxis trials of any antibiotic undertaken in the modern era of COPD management.

5.1.2 COPD subgroups

Three azithromycin chemoprophylaxis trials performed post-hoc, subgroup analyses to identify factors associated with treatment responsiveness to azithromycin. Han *et al*

(n=1142) found no efficacy in current smokers, but greater efficacy in older people or those with milder disease based on FEV_1. There was no difference in treatment response stratified by chronic bronchitis phenotype, sex, concomitant inhaled medication or oxygen use.[31] In a smaller trial (n=92), Djamin *et al* observed no difference in effectiveness between current and ex-smokers or serum CRP levels but suggested that GOLD stage (1 and 2 vs 4) and groups (C vs D) and high blood eosinophils (stratified ≥2% vs <2%) were associated with treatment responsiveness.[32] In contrast, post-hoc analysis of the BACE trial (n=301) showed low eosinophils (stratified <300 vs ≥300μL cells) and high CRP were both associated with greater treatment response to azithromycin. However, of note, no differences were observed in treatment response by age, FEV_1, CRP or blood eosinophil count in **continuous analyses**.[33] A retrospective observational study of 126 COPD patients showed *Pseudomonas aeruginosa* colonisation was a marker of azithromycin treatment responsiveness.[34] Observational studies suggest history of prior exacerbations, COPD control/stability, sex, current smoking, blood eosinophil counts are factors that predict exacerbation risk. Other interacting factors affecting individual patients, such as frailty and multimorbidity, may also influence treatment response and exacerbation risk.[35-38]

5.1.3 Contemporary research

Awareness of contemporary research to this trial is helpful and highlights importance research in this area. The COPERNICOS trial with follow-up of 12 months will evaluate blood eosinophil-guided reduction of inhaled corticosteroid therapy and prophylactic azithromycin. The RELIANCE trial (roflumilast vs azithromycin to reduce COPD exacerbations) aims to recruit 3200 participants with duration of follow-up from 6-36 months.[39,40] Importantly there is not significant overlap between these trials and this trial. More recently, a core outcome set for COPD exacerbations has been published since submission of grant funding application for this trial. These outcomes have been considered and where feasible and pragmatic to this trial have been incorporated.[41]

6 RATIONALE FOR TRIAL

There is uncertainty about how best to use long-term antibiotics in people with COPD to reduce the risk of future exacerbations. Although guidelines are consistent in recommending azithromycin as the prophylactic antibiotic of choice, there are distinct differences between them, notably in eligibility criteria for azithromycin chemoprophylaxis, dose and duration of treatment. This variation, and limited evidence on this topic, makes it challenging for doctors to know how to optimally use this medication in COPD.[1-3] As such, there is wide variation in azithromycin prescribing across the UK. Areas with high COPD prevalence have the highest rates of prescribing in comparison to other antibiotics.[42] Given azithromycin is a valuable antibiotic it should only be prescribed where it has benefit, to avoid unnecessary side effects and reduce risk of antimicrobial resistance (AMR).

In COPD clinical practice, azithromycin is often prescribed for longer than 12 months despite a paucity of evidence to support its use beyond one year. Antibiotic holidays are often used over the summer period when exacerbations occur less frequently and are recommended in some local guidelines.[29] However, we do not know the effectiveness of this approach, or what happens when azithromycin is completely discontinued after a period of use. There is also uncertainty regarding relative benefits or harms of azithromycin chemoprophylaxis in individual patients. Clinicians using azithromycin to reduce COPD exacerbations are unsure if it is safe to discontinue treatment when a patient has been stable for some time and risk recurrence of exacerbations, whether seasonal discontinuation is effective, and whether for an unstable patient; is it dose or duration increases that are needed to gain exacerbation control, or does the patient not actually gain benefit from treatment? Furthermore, contemporary trial data from a large real-world population prescribed azithromycin on longer-term side effects of hearing loss, cardiovascular risk and AMR are urgently needed.

To add wider context, currently ~1.2 million people are living with COPD in the UK and people with COPD are disproportionately affected by health inequalities including frailty and multimorbidity. Exacerbations are a leading cause of hospital admissions, morbidity, and mortality and there are significant increases in COPD-mortality, hospital admissions and bed pressures every winter in the UK, which is why evidence of the effectiveness of seasonal chemoprophylaxis is essential to evaluate. There are ~60,000 prescriptions of azithromycin/month in England, at a cost of ~£450,000/month.[42]

7 TRIAL DESIGN

7.1 Statement of Design

A randomised double-blind, non-inferiority, adaptive, pragmatic trial of 3 parallel arms (continued azithromycin prophylaxis as standard of care vs seasonal discontinuation vs complete discontinuation), to test the strategy of discontinuation of prophylactic azithromycin in patients with stable COPD at high risk of exacerbations. Randomisation allocation will be 1:1:1 using a web-based program.

The target enrolment is approximately 1311 randomised participants (437/arm) recruited from approximately 135 sites across the UK. This is an event-driven trial and the trial sample size estimation is based on number of participants needed to accrue the number of primary endpoint events (n=1242; time to first exacerbation) to statistically determine a minimally clinically important difference (more than 30 days) of experimental arms vs standard of care arm in this non-inferiority trial.

Patients who meet the primary endpoint can continue in the trial to allow collection of secondary endpoints. Based on current assumptions, it is anticipated that a median follow-up of the trial cohort will be approximately 24 months. However, the precise duration of follow-up will be evaluated during the trial and will depend on the rate of recruitment and number and frequency of exacerbations. The TSC (with advice from the IDMC), Sponsor and NIHR will determine the actual duration of enrolment.

The trial is pragmatic, aiming to preserve the ecology of clinical care of COPD patients on azithromycin. The adaptive design of the trial means that a treatment arm can be dropped if futile at interim analysis but remaining arms continue, which is important to ensure as many clinically important questions can be answered in one trial design. The interim analysis is proposed for occurring at approximately 18 months from starting recruitment, but this is dependent on a sufficient number of primary events needed for an interim analysis. The trial design aims to gain robust data on the interventions being assessed (i.e. acute whilst on trial medication/investigational medicinal product ("IMP"))and long-term effects of the interventions being assessed, with long term routinely collected clinical data follow-up of trial participants. Pre-specified subgroup analysis will determine if certain factors impact the effect of azithromycin discontinuation.

7.2 Internal Pilot Study of the OPACE trial

An internal pilot phase of the OPACE trial will test our ability to recruit and randomise participants. It will run for approximately 9 months from first participant first visit (FPFV). Progression from this pilot phase to full trial will be dependent on recruitment and advice from the TSC and NIHR.

7.3 Number of Centres

This is a multi-centre trial. It is anticipated that a large number of centres will be required to fulfil recruitment. It is planned for approximately 135 sites to open for the trial. A combination of primary care (GP surgeries) and secondary/tertiary care sites (hospitals) will

be used. If needed, Participant Identification Centres (PICs) may also be used. If participant recruitment is inadequate, the option to open further participating centres is planned.

7.4 Selection of Participating sites

Criteria for the selection of sites will be determined by the Trial Management Group (TMG) and will be described in a separate CCTU document 'Registration of Interest/Feasibility Assessment Template' maintained in the Trial Master File (TMF).

Only sites fulfilling the trial-specific criteria will be selected to recruit for the trial. Initiation of sites will be undertaken in accordance with CCTU internal processes. Conditions and documentation required for site activation will be detailed on the trial specific Participating Site Initiation Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

Further information on the OPACE trial recruitment targets are provided in the supplementary OPACE trial recruitment plan.

7.4.1 Principal Investigator Responsibilities

The PI's legal responsibilities will be listed in the Participating Site Agreement. It is expected that they attend the site initiation meeting/teleconference, train new members of the trial team in the protocol and its procedures, ensure that the Investigator Site File (ISF) is accurately maintained, disseminate important safety or trial related information to all takeholders within their site, carry out safety reporting within the timelines etc.

7.5 Number of Participants

We plan to randomise 1311 participants in this trial. Full details of the sample size calculation and justification will be detailed in section 15.3.

7.6 Participants Trial Duration

The trial duration for participants will be a median period of approximately 24 months, and will be dependent on acquisition of target primary events and secondary endpoints. Absolute length of the trial (and therefore participant trial duration) will be dependent on advice from the TSC, Sponsor and NIHR and a common end date will be set months in advance. The duration of follow-up will be variable for participants depending on when they are recruited to the trial. Trial participants will continue to be followed-up in the trial, even if they have met the primary endpoint of the trial to enable ongoing collection of secondary endpoints.

7.7 Trial Objectives

7.7.1 Primary Objective

To evaluate clinical effectiveness (specifically time to first exacerbation) of complete or seasonal discontinuation of azithromycin prophylaxis compared to continued azithromycin prophylaxis, as standard of care, in people with stable COPD at high risk of exacerbations.

7.7.2 Secondary Objectives

The secondary objectives will compare acute and long-term effects of discontinuation strategies of azithromycin prophylaxis with continued azithromycin as standard of care (SoC), in people with stable COPD at high risk of exacerbations. Secondary objectives will be assessed over the whole duration of participant follow-up in the trial even though the participant may have reached the primary outcome measure and may therefore include evaluation on trial medication and subsequently off trial medication.

1) Further evaluation of clinical effectiveness defined by effect on exacerbations (specifically number/rate and severity of exacerbations).
2) Health status as measured by symptoms and quality of life.
3) Hospitalisation and healthcare use.
4) Mortality (all-cause, respiratory, cardiac).
5) Adverse events.
6) To determine what factors or patient subgroups impact interventions assessed.
7) To estimate the cost-effectiveness of complete and seasonal discontinuation of azithromycin chemoprophylaxis in people with COPD at high risk of exacerbations.
8) To evaluate adherence.

7.8 Trial Outcome Measures

7.8.1 Primary outcome measure

Time to first COPD exacerbation.

7.8.2 Secondary outcome measures

Data pertaining to secondary outcomes will be collected over the entire trial follow-up (i.e. inclusive of time on IMP and if needed off IMP):

- Number/rate of exacerbations (and differentiation by severity of exacerbations, i.e. requirement of hospitalisation)
- Length of exacerbation-free status
- Antibiotics and/or corticosteroids use for respiratory indication
- Symptoms/impact: CAT score and cough visual analogue score (VAS)
- Health status (quality of life measured by change in EQ-5D-5L)
- Mortality (all cause and specific)
- Healthcare utilisation (for health economic analysis)
- Adverse events of special interest (AESI) (including cardiovascular and hearing- defined as new prescription of hearing aids, liver function test (LFT) dysfunction), serious adverse events (SAEs)
- Sputum culture results, if clinically indicated and sample via routine clinical care to local lab. Record if positive result (i.e. name of organism cultured only, not cfu/ml). If multiple sent, most recent one to trial visit should be used.
- Adherence to trial medication.

8 SELECTION AND WITHDRAWAL OF PARTICIPANTS

The trial will recruit participants who have known COPD, are currently prescribed azithromycin chemoprophylaxis to reduce their risk of COPD exacerbations, and have clinically stable COPD at time of enrolment. A participant can be re-screened for eligibility if they have unstable (exacerbation) COPD at the time of screening, but subsequently become stable.

8.1 Inclusion Criteria

To be included in the trial the participant must:

- Be able and willing to provide informed consent.
- Have an established clinical diagnosis of COPD and be receiving prophylactic azithromycin for ≥ (at least) 3 months to reduce COPD exacerbations.
- Have a self-reported smoking history of ≥ (at least) 10 pack years.
- Be aged >= 40 years.
- Have clinically stable COPD, i.e. no COPD exacerbation for at least 6 weeks.

8.2 Exclusion Criteria

Electrocardiograms (ECGs) will not be a trial assessment nor entry requirement. The presence of any of the following will preclude participant inclusion:

- Known hypersensitivity to any of the trial drugs or excipients.
- Current breast feeding, pregnancy or planned pregnancy during the trial.
- Any medical history or clinically relevant abnormality that makes patient ineligible for inclusion because of a safety concern relating to continuing or discontinuing azithromycin or other considerations.
- Known immunodeficiency requiring immunoglobulin/specific antibody therapy.
- Azithromycin prophylaxis prescribed for non-COPD condition.
- Active participation in COPD CTIMP.

8.3 Treatment Assignment and Randomisation Number

A web-based randomisation/treatment allocation system (i.e. Sealed Envelope; SE) will be used. Stratified blocked randomisation will be used, stratified by number of exacerbations in the previous year (0-1 vs 2 or more). Block sizes will be random.

Participants will be randomised (1:1:1) to one of three interventions. Interventions are:

- **Continued azithromycin (standard of care),**
- **Seasonal discontinuation (azithromycin, 'active' from approximately October-March (i.e. approximately six months- winter), matched placebo from April-September (i.e. approximately six months-summer),**
- **Complete discontinuation (matched placebo)**

Trial medication will be matched as closely as possible within the dosing regimes specified in the protocol to the individual participant's azithromycin prescription regimen.

The randomisation allocation to interventions may adapt depending on interim analysis. For example, an experimental arm may be stopped based on interim analysis results. If so, participants subsequently recruited may be recruited to one of two remaining arms (one of which has to be continued azithromycin (standard of care) or an experimental arm. Please see section 15.2 'Interim Analysis' for further details.

8.4 Method of Blinding

Placebo tablets will be manufactured by Eramol (UK) Limited to be matched to azithromycin film coated tablets. Both active and placebo tablets will be packaged into identical bottles with trial specific Annex 13 compliant labelling and QP released. The bottles will be unblinded until the point of dispensing when a tear-off portion of the label containing the bottle contents (active or placebo) will be removed by a contracted central pharmacy creating a blinded bottle. The trial participants, trial site team (i.e. participant facing team in primary care and hospitals) and members of the central trial team will be blinded to intervention. Pharmacy will be unblinded to enable dispensing according to the randomisation. Once dispensed the packaging and labelling will be identical for azithromycin and placebo. Further details regarding blinding/unblinding are described in the blinding section of the pharmacy manual and TPM.

8.5 Emergency Unblinding

Given that the interventions in this trial include standard of care azithromycin, which participants have already been prescribed for at least three months, or matched placebo, or combination (seasonal), it is anticipated that there will be a low probability of needing emergency unblinding in this trial.

The decision to unblind should be made when knowledge of an individual patient's allocated treatment is required to enable treatment of severe adverse event/s (SAEs), in the event of

an overdose, to enable reporting of a Suspected Unexpected Serious Adverse Reaction (SUSAR).

In the unlikely event that emergency unblinding is needed where possible, the treating clinician should make the decision to unblind. Out of hours requests of unblinding can be made through the OPACE on-call consulting team at the local participating site. This emergency contact number will be on the participant ID card that participants are given to carry upon recruitment to the trial.

Details on how to unblind a patient will be provided in the TPM. All cases of unblinding will be recorded and reported to the CCTU by the local investigator via the SOP pathway to ensure allocation reveal is minimised and trial personnel, trial team members remain blinded. In the event of a SUSAR, the CI and CCTU team will take responsibility for unblinding, and reports submitted to the MHRA via the ICSR Submissions portal.

8.6 Participant Withdrawal Criteria

Each participant has the right to withdraw from the trial at any time. The reason(s) for withdrawal will be recorded on the CRF if this is possible to do so. Although, there is no obligation for participants to provide a reason.

It is always within the remit of the physician responsible for a participant to withdraw a participant from a trial for appropriate medical reasons. Participants may be withdrawn from trial treatment for any of the following reasons as examples:

- 3 or more exacerbations/year
- Unacceptable adverse effects
- Development of serious disease preventing further treatment, or any change in the participant's condition that justifies discontinuation of trial treatment in the clinician's opinion
- Exacerbation in time period from randomisation to receipt of trial medication (home delivered from central pharmacy).

If participants are withdrawn from trial treatment or a participant wishes to stop trial treatment, they will be asked whether they would be willing to remain in scheduled trial follow-up, or if they do not want this, if they allow routinely collected clinical data (i.e. hospital admissions records and mortality) to be used for trial follow-up purposes.

If a participant decides to withdraw from the trial, any data already collected or results from tests already performed will continue to be used in the trial analysis unless explicitly requested by the participant for destruction. The participant should be asked if they would consent to routinely collected healthcare information (for example hospital admissions) to be used for trial purposes until the end of the trial.

8.7 Trial medication stopping rule/early discontinuation of trial treatment

Given the nature of the discontinuation interventions assessed in this trial, a trial treatment (IMP) stopping threshold has been set following discussion with patients and respiratory specialists. This does not affect a participant's right to withdraw from the trial at any time but has been established to gain important information on and off trial treatments for secondary outcomes analyses. The aim of this rule is to balance gaining important information about intervention effects of this trial (acute and long-term perspective of the discontinuations by secondary outcomes), versus the concern of leaving a patient who may have benefited from azithromycin, being on trial medication which may be placebo.

The trial medication stopping rule: participants will stop taking trial medication (IMP) if they have 3 or more exacerbations/year. They will stop IMP as soon as practically possible and can restart their regular azithromycin prescription if advised to by their clinical team.

This trial medication stopping rule does **not** affect the trial's primary endpoint. It is also noted that there is equipoise regarding azithromycin's effect on severe (hospitalised) exacerbations.[5] In the COLUMBUS trial, which included a COPD population cohort similar to that recommended to consider azithromycin prevention treatment for in NICE guidelines, azithromycin reduced exacerbations from a baseline 4/year to 1.94 /year (95% confidence interval (CI) 1.50-2.52) vs placebo: 3.22/year (2.62-3.97).[43] Thus, three or more exacerbations/year seems a reasonable IMP stopping threshold, given the upper CI of exacerbation rates with azithromycin treatment and on discussion of this element of the protocol, was considered an acceptable threshold.

8.8 Treatment of COPD exacerbations and infections during the trial

Where participants need to have treatment for their COPD exacerbations or other infections in the trial, a trial card with information will explain that participants should be treated for their exacerbation or any other infections with non-macrolide antibiotics where at all possible. The trial medication can therefore then be continued during the treatment of the exacerbation/other infection which is in accordance with NICE guidelines[1] and does not require unblinding or temporarily stopping of the IMP.

However, if for any patient reason or it is deemed necessary by the treating clinical team or Principal Investigator that a macrolide antibiotic is required to treat the exacerbation or any infection (for example, patient allergies preclude an alternative class of antibiotics), then the IMP will be temporarily discontinued for the duration of exacerbation or infection treatment and restarted on completion of exacerbation/infection antibiotic treatment.

9 TRIAL TREATMENTS

This is a double-blinded, randomised, placebo-controlled trial comparing routine prescription of azithromycin chemoprophylaxis with placebo, or a combination of azithromycin in winter months (October-March), placebo in summer months (April-September).

The trial prescription will be matched as closely as possible to a participant's current regular prescription at time of trial enrolment (for example if an individual participant is on 250mg or 500mg thrice weekly then their trial prescription will match this). This is because the interventions being assessed in the trial are complete and seasonal discontinuations vs standard of care continued azithromycin treatment as per routine prescription at randomisation, rather than dose and frequency of azithromycin. This also enables the trial cohort to be inclusive of as many COPD participants on azithromycin rather than restricting to a particular dose/frequency treatment regimen.

Further information on trial treatments is provided in the pharmacy manual.

9.1 Treatment Summary

For the purpose of this trial, azithromycin and matching placebo are all considered as Investigational Medicinal Products (IMP)s conducted with a Clinical Trial Authorisation.

The trial is being carried out under a Clinical Trial Authorisation. The drug is therefore only to be used by the named investigators, for the participants specified in this protocol, and within the trial.

9.1.1 Azithromycin

Azithromycin, 250mg or 500mg film-coated tablets for oral administration.

Placebo will be manufactured by Eramol (UK) Limited to be identical in terms of appearance, taste and smell to azithromycin and will be dispensed in containers that are identical in appearance and labelling.

9.1.1.1 *Legal status*

Azithromycin is licensed for the treatment of certain infections. Although recommended as the drug of choice as a chemoprophylaxis indication to reduce the risk of COPD exacerbations in NICE, BTS and GOLD guidelines, and used as such in routine clinical care, azithromycin is not licensed specifically for this indication. Azithromycin will be used in this trial as indicated by its routine clinical care prescription.

9.1.1.2 *Supply*

The Sponsor will supply both active and placebo tablets for this trial and patients will switch from the standard commercial supply to the trial specific supply.

Given the double-blind nature of the trial, sufficient supply of azithromycin film-coated tablets (250mg and 500mg) will be sourced by Eramol (UK) Limited and matched placebo tablets (for both 250mg and 500mg) azithromycin will be made by Eramol (UK) Limited. Eramol will store stock of IMP and will send batches to the central pharmacy for the trial. The pharmacy will dispense IMP upon receipt of a secure notification via the study portal containing associated randomisation information. IMP will be sent by courier or Royal Mail to a participant's address.

9.1.1.3 *Packing and Labelling*

The Sponsor has entered into an agreement with Eramol (UK) Limited to supply packaged and labelled azithromycin 250mg and 500mg tablets and matched placebos for the purposes of the OPACE trial. The product will be provided in tamper proof bottles. Prior to release to central pharmacy, the supplier (Eramol (UK) Limited) will label bottles of azithromycin and placebo with annex 13 compliant labels; each bottle will be supplied with an unblinded tear-off portion of the label which will be removed at the point of dispensing by the pharmacy.

9.1.1.4 *Storage conditions*

Azithromycin tablets (250mg and 500mg) do not require any special storage conditions as per the SmPC.[44] They will be stored under ambient conditions.

9.1.1.5 *Maximum duration of treatment of a participant*

This is an event-driven trial, and the duration of follow-up and therefore potential maximum duration of trial treatment will be determined by monitoring of events and advice from the TSC regarding ongoing follow-up and continuation of the trial. It is anticipated that a participant may be on trial treatment for approximately 24 months. If a participant is recruited early in the trial and does not meet IMP stopping criteria, they may continue on trial treatment until the end of the whole trial. If a participant is recruited later on in the trial and does not meet IMP stopping criteria, they will have a shorter duration of treatment until the end of the whole trial.

9.1.1.6 *Dose*

Dose of azithromycin is as a participant's routine current standard of care prescription at time of enrolment (i.e. 250mg or 500mg). The frequency is as per a participant's standard of care prescription at the time of enrolment. This often is three times a

week. However, it is recognised some participants may have a different dosing regimen (i.e. 250mg daily) and the trial treatment prescription will match an individual's current prescription regimen as much as is possible. Azithromycin for prophylaxis to reduce COPD exacerbations will be a maximum dose of 250mg once daily.

9.1.1.7 *Administration*

The frequency of administration and timing of each dose, will be matched to the participant's routine care prescription at the start of their trial participation. Azithromycin tablets are for oral administration only. Tablets can be taken with or without food. The tablets are recommended to be taken with approximately ½ glass of water and not within 2 hours of taking indigestion remedies.

9.1.1.8 *Known drug reactions (undesirable effects)*

The decision to start azithromycin therapy and the consideration of all potential clinical contraindications, cautions and interacting drugs should already have been considered by the original prescriber. These are listed as a reminder for the prescriber to ensure these are reviewed during the patient's ongoing care whilst in the trial.

The SmPC section 4.3 (Contraindications), section 4.4 (Special warnings and precautions for use), section 4.5 (Interaction with other medicinal products and other forms of interactions) and can be cross-referenced for further information.[45]

Contraindications to azithromycin as per the SmPC, are hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipient listed in section 6.1 of the SmPC.

Potentially serious adverse effects which have occurred with azithromycin include hepatoxicity, pseudomembranous colitis, and clostridoides difficile-associated diarrhoea.

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides including azithromycin, therefore co-administration with other products known to prolong QT should be undertaken with caution.

9.1.1.9 *Interactions with other products and medicines*

All interactions with current medication will have been considered by the original prescriber as part of standard of care prescribing. The below are listed as per the current SmPC but do not require additional monitoring throughout the trial other than what is mandated as part of standard of care.

- Antacids:
    - As per section 4.5 of the SmPC, in patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously. Azithromycin must be taken at least 1 hour before or 2 hours after antacids.

- Digoxin and colchicine: Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

- Ergot derivatives: Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

- Coumarin-Type oral coagulants: There have been reports received potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

- Ciclosporin: Caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.
  Theophylline: As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.

- Azithromycin should be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia, e.g. hydroxychloroquine - see SmPC for more details.

9.1.1.10 *Dose modifications*

No dose modifications will be undertaken during the trial. The dose will match the azithromycin prescription of routine clinical care at the time of trial enrolment.

9.1.1.11 Procedures for monitoring treatment compliance

The trial treatment (IMP) will be taken at home by participants. Compliance will be assessed by asking the participant to estimate their compliance. Participants will be asked to return any unused IMP and empty bottles to their local study site at trial visits.

9.1.1.12 Placebo comparator products

There will be one placebo, matched for 250mg azithromycin tablets, and one matched for 500mg tablets, matched in appearance, that will be identical in prescription, packaging, labelling, dosing and duration of treatment for azithromycin tablets.

The placebo tablets will contain microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate and sodium stearyl fumarate.

9.2 Non Investigational Medicinal Products

No non-investigational medicinal products will be used in this trial. During follow-up, participants should continue to take any prescribed existing concomitant medication, and any new medication prescribed for them but these are not supplied to the participant within this protocol.

9.3 Concomitant Therapy

Any concomitant therapy clinically required will be permitted. However, participants should be instructed to take note of the interactions with other medicines stated within section 9.1.1.9 if they are on those medications.

9.4 Accountability and Dispensing

9.4.1 Pharmacy responsibilities

Please refer to the pharmacy manual for more information. A central pharmacy will be used who will be contracted by the Sponsor to provide storage, dispensing and accountability, and distribution of the IMP to participants. Responsibilities of the central pharmacy will be outlined in a study specific Technical Agreement.

9.4.2 Drug accountability

An agreement between the Sponsor, Eramol (UK) Limited, and Sponsor and the Central Pharmacy will be signed outlining any processes associated with drug accountability. Please refer to the pharmacy manual for more information.

9.4.3 Returns and destruction

Participants will be advised to return IMPs to local trial sites and the IMPs will be destroyed locally according to clinical care SOPs. No returns to the central pharmacy will be made. Please refer to the pharmacy manual for more information.

10 PROCEDURES AND ASSESSMENTS

Detailed information related to this section of the protocol are outlined in the sub-sections 10.1 to 10.6 below, and provided in the TPM.

10.1 Participant Identification

Potentially eligible participants will be identified by screening medical records or through clinic consultations, and then given or sent an invitation letter and participant information sheets by the local PI/research team. This will ask if they would like to learn more about the trial or if they do not want to be contacted about it again. Further trial information participant materials including signposting to the trial website where a range of resources regarding the trial will be posted and a video(s) about the trial will be available too. Alternative means of participant identification maybe through participant's self-interest in the trial via its website. This will entail potential participants contacting their most local participating site via details on the trial website.

10.2 Consent

The Informed Consent Form (ICF) must be approved by the Research Ethics Committee (REC) and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator or designee must ensure that each trial participant, is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

The investigator or their designee will obtain written informed consent from each participant before any trial-specific activity is performed. The ICF used for this trial and any change made during the course of this trial will be approved by the REC. One copy of the ICF will be kept by the participant, one will be retained by the research site; original to be kept in medical notes.

If consent is conducted in person, both the investigator or their designee and the participant shall sign and date the ICF. In the event that consent is obtained remotely, the participant only shall sign and date the consent form, and the investigator or designee will sign and date the corresponding Confirmation of Consent Process form. Both these forms will be

required for full evidence of consent. Further details of the remote consent procedure can be found in the TPM.

The consent will include permission for:

- electronic record linkage via NHS Digital to the Office of National Statistics (ONS) for mortality and hospital episodes statistics (HES)
- access by the research team to hospital records where necessary for the purposes of trial outcome measures.
- central coordinating trial team and/or central pharmacy will have access to participant details to enable conduct of the trial if required (i.e. for coordination of home delivery of medication).

For the purpose of oversight and audit inspection of the trial, the lead site central coordinating team will be sent a copy of the ICF (and additionally Confirmation of Consent Process form where remote consent process is used). These forms will be sent to check they are being completed correctly. The lead site central coordinating team will destroy the copy of ICF (and Confirmation of Consent Process) as per NHS confidential waste standard, once the checks have been made. Forms will be sent using secure transfer methods (e.g. nhs.net to nhs.net email)

Should a participant require a verbal translation of the trial documentation during the consent process by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators.

If the trial requires participant-facing documentation in a different language (other than English), the translation and back translation documents need to be reviewed and approved by the Sponsor prior to use. All sections of the approved documents must appear in the translation. The translated version must be appropriately dated and include version control.

Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial will be communicated to the participant as soon as possible. This new information will be provided either verbally over the telephone or in writing by post.

Additional consent for ancillary studies
Participants will be asked if they consent to receive invitations and information for any further associated ancillary/substudies studies that may arise from the OPACE pilot phase.

10.3 Screening Evaluation

Inclusion and exclusion criteria as per sections 8.1 and 8.2 will be used in screening evaluation.

Screening and baseline visit (i.e. trial visit 1) can be performed at the same visit if required. Information regarding reasons why patients were not eligible for the trial will be collated. If the patient was eligible but declined to take part, this will also be recorded on screening logs.

A participant can be re-screened for eligibility for participating in the trial during the active recruitment phase of the trial project, if they are experiencing a COPD exacerbation at the time of screening, but subsequently become stable in their COPD, for example.

10.3.1 Screening Assessments

There are no specific screening assessments as part of the trial and eligibility is determined by inclusion and exclusion criteria. Assessment of eligibility will be undertaken at screening

and re-evaluated as needed prior and within baseline visit and consent consultation. There is no specific time period from screening to baseline visit. ECGs will not be used during screening of potential participants, since participants are already prescribed and on azithromycin via a clinical care pathway. ECGs may be undertaken as part of routine clinical care at any time during the trial if clinically indicated. Trial specific assessments will only be conducted after participants have given written informed consent.

Current breast feeding, pregnancy or planned pregnancy during the trial is an exclusion criterion of the trial. Pregnancy testing will not be conducted at screening.

10.3.2 Participant Registration/Randomisation

Following informed consent, each participant will be registered and provided with a unique trial ID. Participant registration is needed before any other visits and data collection can be scheduled. Randomisation will then take place via Sealed Envelope (SE). Further information on data collection variables and trial assessments are provided in the TPM.

10.4 Trial Assessments

This is a pragmatic trial and as such the assessments included are to answer the trial objectives only and preserve ecology of standard of care practice as much as possible. Medical history, smoking history and drug/medication history will be recorded in the trial based on participant reported information and may be corroborated with healthcare records. This will include COVID and influenza vaccination status and medications that participants are prescribed including for their COPD.

Exacerbations are a key part of the outcome measures of the trial. The exacerbation history of a patient at baseline is also important. Further detail regarding aspects of exacerbations are provided below:

10.4.1 Exacerbation definition

The ATS/ERS guideline definition of a COPD exacerbation will be used: i.e. a worsening of patient's COPD symptoms beyond day-to-day variability sufficient to warrant a change in management. The minimum change in management for definition of an exacerbation for the trial is requiring treatment with additional antibiotics and/or oral corticosteroids.[45] A minimum of two weeks between exacerbations is necessary to consider them as separate exacerbations.[46] Exacerbation severity will be ascertained (i.e. moderate is use of additional antibiotics and oral steroids, severe is requirement of hospitalisation).[1, 45, 46]

10.4.2 Exacerbations history at baseline

Participants will be asked how many COPD exacerbations they have experienced in the last 12 months and whether any of those required hospital care.

10.4.3 Exacerbations record during the trial

Participant reported and recall of exacerbation events are highly reliable.[47,48,49] Exacerbations will be participant reported throughout the trial (not tied to scheduled visits) and dates determined to the nearest calendar day. Participants will be advised how to report/notify the local trial team of their exacerbation details as they happen for an event. A participant COPD exacerbation diary card will also be provided to enable participants to record the details of each exacerbation. At scheduled visits, exacerbations information will also be collected, and details confirmed or corroborated if needed.

Participants' relative/next of kin/healthcare team can also contact the trial team if needed to let them know of the exacerbation if the participant is too unwell.

If a participant has 3 or more exacerbations per a year period from starting their trial medication, the trial team will review this information to see if the trial medication stopping threshold is met and if the IMP should be discontinued. If so, the participant and their healthcare provider will be informed so they can decide if the participant should restart their routine clinical care azithromycin prescription.

Further information on the IMP stopping rule and treatment of exacerbations and infections during the trial whilst on IMP are provided in sections 8.7 and 8.8 respectively.

10.4.4 Exacerbation within period from randomisation to receipt of trial medication

There will likely be a short delay from the time of randomisation to receipt of trial medication since trial medication will be home delivered. All participants will be advised to remain on their current clinical prescription of azithromycin until receipt of trial medication and then to start trial medication. If a participant exacerbates prior to receipt of trial medication it is likely this will be similar across all three treatment arms.

10.4.5 Data collected from healthcare records

If available, specific data from participant's healthcare records relevant to this trial's objectives will be recorded in the CRF at baseline visit. These data will also likely be participant reported and where possible data will be corroborated from the participant with the healthcare records.

Data collection from healthcare records and/or participant reported that will be recorded at baseline include**:**

- Demographics (age, sex, ethnicity) and contact details
- Exacerbations history (in previous 12 months)
- Medical history including cardiovascular disease history and comorbidities
- Smoking history/status, i.e. current or ex-smoker
- Drug/medications including azithromycin duration of use and current prescription
- Most recent eosinophil blood count, historic highest and lowest eosinophil blood count (≤ 3 years)
- Information from computerised tomography (CT) of the chest (most recent), if available.
- Spirometry result if available (for example, FEV_1 (L)/FEV_1 %, FEV_1/FVC)
- Sputum result if available (≤ 12 months)-if positive culture.(Please see TPM).

10.4.6 Sputum result

Sputum testing will be performed as part of routine standard of care and is not a trial assessment. If a sample is clinically indicated and sent to local lab via routine clinical care during the trial, the result will be recorded in the trial only if it is culture positive and if so, the most recent sample to the visit date will be recorded if multiple positive samples are available.

10.4.7 Height, weight and BMI

Where possible height and weight measurements will be carried out using weighing scales and a wall height chart/stadiometer. If this is not possible, height and weight will be obtained from patient recall or medical records. BMI will be calculated from the height and weight.

10.4.8 Blood test

The full blood count (FBC) at baseline will be obtained (~4 mls) unless there is one available from the last six months. It is recognised there can be a delay in organising a separate blood test appointment if unable to do within baseline visit. This will not delay the participant starting trial medication and this information will be recorded. It is recognised this assessment is also dependent on impact of COVID-19 pandemic situation at the time of the trial.

10.4.9 Spirometry

Basic spirometry may be performed at baseline unless there is a most recent spirometry result in the records from the last 2 years. Spirometry will be performed in accordance with local standard of care practice/standard operating procedures (including GP practices if able to do).[50] Post bronchodilator lung function will be used. If a participant is unable to perform spirometry, it will not preclude them from participating in the trial, and scheduling a separate appointment for spirometry should not delay the participant starting trial medication and this information will be recorded.

Questionnaires

Individually, each questionnaire should only take a few minutes to complete, but may take up to 20 minutes to complete in total. The questionnaires have been selected for their ease and simplicity of use and/or are validated assessments used in clinical care and/or research.

10.4.10 Health related quality of life (EQ-5D-5L) (approximately 2 mins)

Health related quality of life data will be captured at baseline, and during trial follow-up. Assessments will be undertaken using EuroQoL 5D-5L (EQ-5D-5L) Index that has been used widely in COPD. EQ-5D-5L was developed as a utility questionnaire and addresses mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The completed instrument can be translated into quality-of-life utilities suitable for calculation of QALYs through the published UK tariffs.[51]

10.4.11 COPD Assessment Tool (CAT) (approximately 5 mins)

CAT will be assessed at baseline and during trial follow-up. This is a validated short (8 questions) simple patient completed questionnaire, with good discriminant properties, developed for use in routine clinical practice to measure the health status of patients with COPD. Despite the small number of component items, it covers a broad range of effects of COPD on patients' health. Studies have shown that it is responsive to change and to treatment.[52]

It takes a few minutes to complete and can be completed on paper or online via the CAT website. The result can be either saved and emailed or printed out.

10.4.12 Cough visual analogue scale (VAS) (approximately 1 min)

Cough VAS (0-100mm) will be assessed at baseline and during trial follow-up. It is a simple, quick patient completed assessment of cough used to assess cough severity in patients with chronic cough, whereby patients mark from 'no cough' (0mm) to 'worse cough ever' (100mm) on a linear scale. Cough VAS scale is highly repeatable over a 2-week period in patients with cough due to COPD.[53]

10.4.13 Frequent productive cough (approximately 2 mins)

The presence of frequent productive cough (symptoms associated with chronic bronchitis) will be assessed at the baseline visit by questionnaire - from the two questions on cough in

the CAT score (10.4.12) and two questions on cough from the St George's Respiratory Questionnaire (SGRQ)-COPD.[54,55] Further information will be provided in the TPM.

10.4.14 Patient health questionnaire-2 (PHQ-2)- depression screen (approximately 2 mins)

This component will be used to screen for depression at baseline and comprises the first 2 items of the PHQ-9 assessment. It is based on recall over the last two weeks and is scored from 0-6. A higher score indicates increased likelihood of a depressive disorder and need of further investigation. A score of 2 or higher may suggest a possible depressive disorder. The PHQ-2 has been validated in many studies and has shown sensitivity of 83% and specificity of 92%. It is often used in primary care to screen for depression and is quick and easy for patients to fill out.[56] If the PHQ-2 screening test is suggestive of a possible depressive disorder and this is not already a known diagnosis, the participant will be advised to see their GP about it. Any clinically relevant findings from trial participant that are deemed to require follow-up will be communicated to the GP. Please refer to the TPM.

10.4.15 Generalised Anxiety Disorder-2 (GAD-2)- anxiety screen (approximately 2 mins):

This is a 2-item instrument that is used to screen for anxiety and will be used at baseline. It is often used in primary care as it is simple and easy to do. It comprises the first 2 items of the GAD-7 questionnaire. It is scored from 0-6 with a higher score indicating an underlying anxiety disorder. A score ≥ 3 is suggestive of an underlying anxiety disorder and need for further investigation. The GAD-2 has been validated in many studies and has reasonable sensitivity of 83% and specificity of 92% similar to the GAD-7.[57] If the GAD-2 screening test is suggestive of a possible anxiety disorder and this is not already a known diagnosis, the participant will be advised to see their GP about it. Please refer to the TPM.

10.4.16 Healthcare usage

Information regarding healthcare usage (hospitalisation and primary care consultations for example) will be recorded.

10.4.17 Adherence

Adherence will be evaluated during trial follow-up by estimated compliance, whereby participants will be asked to return trial bottles and unused medication to the trial research team at their appointment(s).

10.4.18 Adverse events/SAEs

Adverse events (AEs) and SAEs will be assessed at baseline and during trial follow-up. AEs will be recorded within the medical notes; SAEs will be reported to the central OPACE trial team for CI review. For more information see section 11.

10.4.19 Self-Rated Health Status (SHS) (approximately 1 min)

This will be assessed at baseline and at the end of trial and will be used in the Study Within a Project (SWAP) as described in the Appendix B. The SHS is a one question assessment of health status recommended by NICE as a screening tool for frailty in patients. It asks patients to rate their health on a scale of 0-10. A score of 6 or less indicates frailty.[19, 58]

10.4.20 Clinical Frailty Scale (CFS) (approximately 1 min)

This will be assessed at baseline and end of the trial as part of the SWAP as described in Appendix B. The Clinical Frailty Scale (CFS) is a tool used in clinical practice in older patients to provide an assessment of capability (in last two weeks) which may be helpful to indicate frailty. It can be conducted by any appropriately trained healthcare professional.[59]

10.4.21 Electronic Frailty Index (eFI) (approximately 2 min):

This forms part of the SWAP (Appendix B) and will be calculated at baseline and end of trial if this is possible and sufficient data recorded to enable this. The electronic frailty index (eFI) uses existing information from the local healthcare record and is recommended by NHS England to be used as a tool to indicate frailty. The eFI is based on 36 deficits and is calculated based on the sum of deficits an individual may have/total number of deficits (i.e. 36).[60, 61] It can be calculated by software automatically from read codes in the primary healthcare record and it is recommended for GPs to do this. Whether sites will be able to easily have access to a participant's eFI is unknown, and it will be calculated based on data entered into the trial database, if sufficient data is recorded to enable this.

10.4.22 Cambridge MultiMorbidity Score (CMMS) (approximately 1 min)

This forms part of the SWAP (Appendix B) and will be calculated at baseline and end of trial if this is possible and sufficient data recorded to enable this. The Cambridge Multimorbidity score (simplified version based on 20 weighted conditions) has been validated to predict key health outcomes based on morbidities. It will be calculated based on data entered into the trial database, if sufficient data is recorded to enable this.[62]

Questionnaires/data collected from 10.4.19-10.4.22 is for the SWAP (study within a project) - see Appendix B.

10.5 Timing of assessments/trial visits

All trial visits can be scheduled to coincide with routine clinical appointments and can be in person or remote, depending on the participant's preference. Ideally, the baseline visit and visit at 12 months will be in person but can be arranged via alternative approaches if participant preference and if needed due to the pandemic situation, or if routine clinical appointments are generally not being conducted in person. Any tests that are not possible to be performed as part of the visit (i.e. blood test) can be organised via the routine clinical pathway. Recruitment of participants who may have limited mobility or who live some distance from the study site, can be carried out during a home visit if the local trial team are able to provide home visits. Remote visits may mean a telephone consultation or using video technology if this is used in routine clinical appointments. Participants can also use email and post in addition to telephone communication with the trial team if needed for different reasons.

After obtaining informed consent, the following visits/follow-ups for trial participants are planned. The trial follow-up period will be a variable duration depending when the participant is recruited to the trial. It is anticipated for the trial cohort as a whole, to have a likely median follow-up of 24 months. However, this is dependent on guidance during the trial from the TSC. A common end date of the trial will be set during the trial, several months in advance to facilitate end of trial follow-up.

- **Baseline/recruitment visit**
- **1 week (+/-7 days):** telephone call to check received trial medications.
- **3 months (+/-14 days):** telephone call follow-up
- **6 months (+/-14 days):** telephone call follow-up
- **12 months (+/-14 days):** in person follow-up/remote can be arranged if needed
- **Then every 6 months approximately (telephone or in person alternate) (+/-14 days) until end of trial**

- **After participant's scheduled follow-up has completed:**
  Hospital episode statistics and ONS data (for mortality) will be collected for participants over the OPACE trial period until the specified common end date of the trial, if available. These data will be analysed for clinically important outcomes, i.e. hospital admissions and mortality.

- **Additional follow-up if needed:** If a participant has any medical concerns or issues related to participating in the trial, they can raise these with the trial team who will arrange a further follow-up with the trial team if indicated, or advise to seek help via their GP/specialist/emergency medical help if appropriate.

An approximate +/- 14 days window for each follow-up visit and telephone follow-up is permitted. These are provided as an approximate window for conduct of follow-ups. It is recognised that for various reasons it may be difficult to schedule within these specific time windows. If so, follow-up should be scheduled as close to the time window as possible.

In the event that a participant is unable to attend a scheduled assessment visit because of an acute illness e.g. exacerbation of COPD, or other reason, the visit will be appropriately postponed, ideally within 6 weeks of scheduled assessments. However, it is recognised for different reasons this may be longer.

10.5.1 Baseline visit (visit 1)

Following obtaining informed consent, data will be collected for the following information required to answer the trial objectives.

Participants in their baseline visit will also be given/sent out in the post a trial card with relevant information on it, which is important for them to present to healthcare providers to let them know of their participation in the trial if needed.

Further information regarding exacerbations management is provided in section 8.8 and will be highlighted to participants at baseline and in trial information. The process of participant notification of exacerbations will be detailed in the TPM. As per section 10.4.3, participants will be provided with a trial diary card to record exacerbations and advised how locally to notify the trial team to let them know if they have had an exacerbation(s) during the trial.

The Participant Information Sheet and the Participant ID trial card will provide participants information on how they can contact the trial team if they have any concerns regarding their trial participation, trial medication or exacerbations.

Data collection from healthcare records and/or participant reported that will be recorded at baseline visit are stated in Section 10.4.5.

Assessments performed to include:

- Height
- Weight
- BMI
- Exacerbation history, medical history

- Questionnaires:
  - Disease related health status (COPD Assessment Tool (CAT), chronic bronchitis, cough visual analogue score (VAS))
  - General health (anxiety-GAD-2, depression-PHQ-2, frailty-SHS)
  - Health related quality of life (EQ-5D-5L)

- Adverse events (AEs) and serious adverse events (SAEs). Please see section 11.3.
- Spirometry (unless there is a result available from within the previous 2 years). FEV_1/FVC will be recorded.
- Blood test-FBC (unless there is a result available from the last 6 months)
- SWAP: (evaluation of SHS and CFS, data recorded to enable calculation of eFI and Cambridge multimorbidity score)

10.5.2 Week 1 (+ 14 /- 7 days) telephone call

- Confirm participant is content to continue to participate in the trial.
- To check received trial medication, understands how to take it and date when started trial medication and check trial medication compliance.
- Assessment of AEs and SAEs. Please see sections 11.4 and 11.5.

10.5.3 Telephone follow-up (3, 6 months (+/- 14 days))

- Confirm participant is content to continue to participate in the trial.
- Record any exacerbations details/confirmations; if information regarding exacerbations has already been provided. Healthcare usage.
- Questionnaires
  - CAT score
  - Cough VAS (6 months only)
- Check trial medication compliance-if still on trial medication
- Assessment of adverse events and SAEs. Please see sections 11.4 and 11.5

10.5.4 Visits follow-up (12 months (+/- 14 days), and ~6 monthly (alternate visit or telephone) until end of trial)

- Confirm participant is content to continue to participate in the trial.
- Check smoking status (every 12 months)
- Record any exacerbations details/confirmations; if information regarding exacerbations has already been provided. Healthcare usage.
- Questionnaires
  - CAT score, (every 6 months)
  - Cough VAS, EQ-5D-5L (every 12 months)
- Check trial medication compliance if still on trial medication
- Assessment of adverse events and SAEs. Please see sections 11.4 and 11.5
- SWAP end of trial: SHS, CFS, data to enable calculation of eFI and Cambridge multimorbidity score

10.6 Schedule of Assessments

		Baseline	Trial follow-up, anticipated approximately median 24 months				
Visit		1*	Telephone call•	Telephone follow-up•	Telephone follow-up•	2*	Follow-up** /end of trial
	Screening	Day 1	1 week	3 months	6 months	12 months	~6 monthly
Pre-consent screening and approach	X	X					
Informed consent		X					
Baseline assessments (Eligibility confirmation)		X					
Demographics		X					
Smoking history		X					
Smoking status		X				X	X
Medical history including cardiovascular disease history		X					
Baseline exacerbations history over last 12 months		X					
Azithromycin duration of use & current prescription		X					
Concomitant medications		X					
Healthcare usage				X	X	X	X
Height & weight if not done within last 2 years^		X					
Spirometry^^		X					
Blood test (FBC)°		X					
Health records access (lab eosinophils, CT chest, sputum, spirometry reports) if available		X					
Questionnaires							
(CAT) score		X		X	X	X	X

EQ-5D-5L		X				X	X
Cough VAS score		X				X	X
Chronic bronchitis		X					
GAD-2		X					
PHQ-2		X					
SHS⊗		X					X
CFS⊗							X
eFI⊗							X
CMMS⊗							X
Randomisation		X					
Adherence			X	X	X	X	X
Adverse event assessments		X	X	X	X	X	X
Exacerbations report during the trial◊			X	X	X	X	X
			Exacerbation notification throughout trial follow-up. Decision whether to stop trial IMP will need to be made (i.e. if 3 or more exacerbations/year).				
IMP home delivery#		X			X	X	X
Sputum results			if sent				

*can be in person or via remote communication means if needed. (A separate consent consultation in person or remotely prior to Day 1 can be arranged if necessary)

**can be via telephone or other communication means if needed. Given variable duration of follow-up for the trial cohort, not all participants will have the same number of visits/follow-up. The common end date of the trial will be set several months in advance. This will allow sufficient time for an end of trial visit to be arranged within approximately 6 months of the trial common end date for all participants recruited. Participants recruited early in the trial, will have a higher number of follow-ups until end of trial, compared with participants recruited late in the trial, since these participants are recruited closer to the common end date of the trial.

^Height and Weight: if not able to do height and/or weight assessment during visit, reported height and/or weight can be recorded if a remote consultation and/or unable to do during the visit. Height and/or weight measurements can be done at a subsequent trial follow-up/clinical follow-up if not able to perform currently, but maybe able to at a later time.

^^Spirometry. Spirometry performed if participant able to, pending clinical service capacity to provide this and impact of COVID-19 pandemic situation at the time of the trial. Have allowed ~1month from baseline assessment and will not preclude randomisation or start of trial medication. If done in last 2 years approximately can use.

◊Exacerbations report during the trial. Participants will be advised how to do this depending on local practice and record in participant diary card.
°can be used if done clinically in last 6 months
#currently planned for 6 months delivery, delivery schedule may change.
⊗part of study within a project (see Appendix B).

10.7 Long-Term Follow-up Assessments

After the active treatment phase of the trial has completed, participants' long term (survival data and hospitalisations) data will be collated until trial end date. This will be via NHS Digital and ONS analogous services in devolved administrations.

10.8 End of Trial Participation

Participants will have finished their active trial participation when they complete their end of trial visit. Participants will return to standard of care following their participation in the trial.

10.9 Trial Restrictions

Trial restrictions in terms of interactions with other therapies are described in section 9.1.1.9.

Pregnancy
Section 4.6 of the SmPC states that azithromycin should only be used during pregnancy if the benefit outweighs the risk.

11 ASSESSMENT OF SAFETY

OPACE trial is a Type B study. Azithromycin is a licensed medication and is recommended as the chemoprophylaxis of choice in guidelines (NICE, GOLD, BTS) for reducing the risk of COPD exacerbations. The dose and frequency used in this trial is as per routine clinical care prescribing.

11.1 Definitions

11.1.1 Adverse event (AE)

Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Please note: Recording of all adverse events must start from the point of Informed Consent regardless of whether a participant has yet received a medicinal product. AEs will be recorded in participant's medical notes.

11.1.2 Adverse reaction to an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or The Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

11.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety information (RSI). When the outcome of the adverse reaction is not consistent with the applicable RSI, this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on participant/event outcome or action criteria.

11.1.4 Serious adverse event or serious adverse reaction (SAE / SAR)

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing inpatient hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is an important medical event - Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious'.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

11.1.4.1 Operational definitions for (S)AEs

In this trial

- SAEs will be reported from the time a participant consents to join the trial until the end of trial, if a participant remains on trial medication. Participants who withdraw from taking trial medication will have SAEs reported from the time the participant consents to join the trial until 28 days after ceasing trial medication. Participants who never start taking the trial medication will have SAEs reported for 28 days from the time they consent to join the trial.
- All adverse events and adverse reactions will be recorded for the same period of time described above.
- Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will **not** be considered, recorded or reported as an SAE.
- Complications occurring during such hospitalisation will also not be considered, recorded or reported as an SAE – unless there is a possibility that the complication arose because of the trial medication (i.e. a possible adverse reaction).
- Exacerbations of COPD, pneumonia or hospital admissions as a consequence of exacerbations of COPD or pneumonia will **not** be considered or reported as AEs or SAEs because they are primary and secondary outcomes for the trial. These will be recorded as part of the trial outcomes.

All other SAEs (including SARs) should be reported to the lead site trial office (see front cover of the protocol and SAE Form for SAE reporting contact information).

11.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information.

11.1.6 Reference Safety Information (RSI)

A list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which Serious Adverse Reactions (SARs) require expedited reporting.

The RSI is contained in a clearly identified section of the Summary of Product Characteristics (SmPC) or the Investigator's Brochure (IB).

For this trial, the Reference Safety Information is:
Section 4.8 of the SmPC of Azithromycin 250mg film coated Tablets (Accord-UK Ltd) approved by the MHRA for use in this trial.

11.1.7 Participant Reporting Duration

The Sponsor expects that adverse events are recorded from the point of Informed Consent regardless of whether a participant has yet received a medicinal product to end of active trial follow-up in the trial.

11.2 Expected Adverse Reactions/Serious Adverse Reactions (AR/SARs)

All expected Adverse Reactions are listed in the latest MHRA approved version of the RSI as specified in section 11.1.6. This must be used when making a determination as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as per section 11.5.

11.3 Expected Adverse Events/Serious Adverse Events (AE/SAE)

Exacerbations of COPD or hospital admissions as a consequence of exacerbations of COPD will **not** be considered as AEs or SAEs because they are primary and secondary outcomes for the trial. These will be recorded as part of the trial outcomes, and therefore not reported as AEs or SAEs.

Adverse events of special interest (AESI) that will be evaluated in the trial include those below. These may also require SAE reporting.

- New major adverse cardiovascular events (MACE):
  Myocardial infarction
  Stroke
  Cardiovascular death
  Development of arrhythmias
  Hearing (for example new prescription of hearing aids)
  LFT dysfunction

These will be recorded separately to all other AEs, to enable ease of data analysis.

11.4 Evaluation of adverse events

Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event (causality) and severity.

11.4.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 11.1.4. This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction.

11.4.2 Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible

time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be trial drug related.
Definitely, Probable and Possible causalities are considered to be trial drug related.

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the CRF.

11.4.3 Clinical assessment of severity

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity

Severe: Significant impairment of functioning; the participant is unable to carry out usual activities and / or the participant's life is at risk from the event.

11.4.4 Recording of adverse events

Adverse events and adverse reactions should be recorded in the medical notes and the appropriate section of the CRF and/or AE/AR log. Serious Adverse Events and Serious Adverse Reactions should be reported to The Sponsor as detailed in section 11.5.

11.5 Reporting serious adverse events

Each Principal Investigator and designated team member needs to record all adverse events and report serious adverse events to the CI using the trial-specific SAE form within 24 hours of their awareness of the event.

SAE reporting for the OPACE trial will not require information regarding SAE treatment or concomitant medications of the participant to be reported, unless the SAE is related to concomitant medication. If the SAE is deemed related to concomitant medication, then the name, dose, frequency of the concomitant medication will need to be reported.

SAEs that are deemed to be SARs or SUSARs will need to include SAR/SUSAR treatment details and relevant concomitant medications.

The CI is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SAEs to The Sponsor within 24 hours of becoming aware of the SAEs. The Sponsor must keep detailed records of all SAEs reported to them by the trial team.

The CI is also responsible for prompt reporting of all serious adverse event findings to the competent authority (e.g. MHRA) of each concerned Member State if they could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the risk to benefit ratio of the trial
- alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC.

The completed SAE form should be emailed to the email address found on the OPACE SAE form cover page and the front cover of the protocol.

11.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Please see section 11.1.6 for the Reference Safety Information to be used in this trial.

11.6.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the CI. The CI must report all the relevant safety information previously described, to the

- Sponsor
- competent authorities in the concerned member states (e.g. MHRA)
- Ethics Committee in the concerned member states

The CI shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

11.6.2 When to report?

11.6.2.1 Fatal or life-threatening SUSARs

All parties listed in 11.6.1 must be notified as soon as possible but no later than **7 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional **8 calendar days**.

11.6.2.2 Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in 11.6.1 as soon as possible but no later than **15 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

11.6.3 How to report?

11.6.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:
a) A suspected investigational medicinal product
b) An identifiable participant (e.g. trial participant code number)
c) An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
d) An identifiable reporting source

Also when available and applicable:

- A unique clinical trial identification (Clinical Trials.Gov number or in case of non-European Community trials The Sponsor's trial protocol code number)
- A unique case identification (i.e. The Sponsor's case identification number)

11.6.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate

information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant and significant safety information should be reported as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

11.6.3.3 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

11.7 Pregnancy Reporting

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/fetus. If the outcome meets the serious criteria, this would be considered an SAE and should be reported within 24 hours of the site trial team becoming aware. See section 11.5 for SAE reporting procedure. Azithromycin is a licensed medication with an established safety profile and has already been prescribed as part of clinical care. Azithromycin is a macrolide and as an antibiotic class; they are generally considered safe to take during pregnancy where clinically indicated.

12 TOXICITY – EMERGENCY PROCEDURES

Information for this section has been taken from section 4.9 'Overdose' of the SmPC for reference.

Adverse events experienced in higher than recommended doses of azithromycin were similar to those seen at normal doses.

Symptoms
The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Treatment
In the event of overdose the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

13 EVALUATION OF RESULTS (DEFINITIONS AND RESPONSE/EVALUATION OF OUTCOME MEASURES)

13.1 Response criteria

13.1.1 Exacerbations

Primary endpoint is time to first exacerbation.

Secondary endpoint is number/rate and severity of exacerbations (i.e. moderate and/or severe). These will be patient reported and recorded in the database.

13.1.2 Survival

This will be measured from the date of randomisation and will be reported for all deaths. The cause of death is to be recorded in all instances where possible. All-cause mortality, respiratory/COPD-related and cardiovascular mortality will be collated.

13.1.3 Quality of life, anxiety and depression

EQ-5D-5L will be used to assess quality of life. GAD-2 and PHQ-2 will assess levels of anxiety and depression.

13.1.4 Symptoms

These will be assessed by the CAT score and cough VAS.

The self-rated health status (SHS) will assess level of frailty in participants.

Healthcare usage for their COPD will be assessed throughout their trial follow-ups.

14 STORAGE AND ANALYSIS OF SAMPLES

In cases of participant withdrawal from the trial, any data or samples already collected or results from tests already performed will continue to be used in the trial analysis. No research biological samples are taken in the OPACE trial for storage. The FBC blood test performed at baseline will be ordered and sent via routine clinical NHS laboratory pathways for local sites and the relevant result from the blood test recorded in the trial database. Similarly for any sputum sample sent if clinically indicated, this will be ordered and sent via local clinical care pathways and the most recent result of a culture if positive will be recorded in the trial database.

15 STATISTICS

15.1 Statistical Methods

A Statistical Analysis Plan (SAP) will be written and approved by the TSC and NIHR. A version of the SAP outlining the key aspects of the primary analysis, will be produced before any efficacy data is examined by the independent data monitoring committee (iDMC), TSC, or any members of the trial team. An interim SAP will be produced before any interim analysis is performed.

The primary endpoint is time to first exacerbation. The experimental treatments are complete discontinuation, seasonal discontinuation, and the control arm is continued azithromycin (this is standard of care). The hazard ratio comparing the two experimental arms to control will be estimated using a Cox proportional hazards model, adjusting for pre-randomisation factors of exacerbations history (number in preceding 12 months) and recruitment site. The consensus decision of the project team was that recruitment site and history of previous exacerbations (given this is the strongest predictor of exacerbations) are appropriate pre-specified covariates. Formal inference will compare the 1-sided confidence interval to the non-inferiority margin of a hazard ratio of 1.25. If the interval lies entirely below 1.25 then a conclusion of non-inferiority will be made. The confidence intervals will be at a 97.3% level, to adjust for there being two comparisons, and thus preserve an overall 5% significance level. The primary analysis will be an Intention to Treat analysis.

For the panel of subgroup factors to consider (section 15.1.1-15.1.2), the analysis will estimate the main effect and a treatment-subgroup interaction on the hazard ratio scale, adjusting for baseline covariates used in the primary analysis. This will be carried out in a univariate fashion, looking at each subgroup individually. Potentially, a multivariate model will be developed to include multiple subgroups simultaneously and provide a risk score. Standard 95% confidence intervals for the estimated subgroup-treatment interaction hazard ratio will be the primary focus. Multiple testing would preclude making strong claims of formal statistical significance; and any personalised treatment strategy would need to be validated in future research.

Secondary endpoints will be analysed using a similar regression methodology, as suitable for the nature of the endpoint (binary, categorical, continuous, time-to-event). The rate of

exacerbations will be evaluated by dividing number of exacerbations by person-years of follow-up and will be analysed with both Poisson and negative-binomial analyses.

Missing data will be quantified for each endpoint broken down by treatment arm. The reference analyses will assume missing at random, conditional on the baseline covariates used for adjustment. Should the rate of missing data exceed 10%, then multiple imputation will be used in sensitivity analyses that consider alternative assumptions incorporating selection bias.

15.1.1 Pre-specified subgroup analysis

The aim of this subgroup analysis is to identify factors that may practically support front line clinicians in shared decision making for individual patients. Selection of subgroup variables have been considered in-depth based on post-hoc evidence of azithromycin prophylaxis trials in COPD, and consideration of generalisability to clinical practice. The limitations of subgroup analyses are recognised. We have tried to limit multiplicity and plan to undertake and report subgroup analysis as per recommended criteria.[63] Subgroup analysis will be performed for the trial's primary endpoint, as well as secondary outcomes of exacerbation rate (including severe exacerbations analysed separately) and side effects/risks, evaluated on IMP.

15.1.2 Top priority subgroup analysis:

- **Exacerbation history (number in last 12 months):** Strongest predictor of future exacerbations.[35]
- **FEV_1 %:** In two trials milder airflow obstruction was associated with greater treatment efficacy of azithromycin in COPD, although trial populations may not be reflective of real-world COPD patients prescribed azithromycin. (i.e. one trial-not frequent exacerbators, other included GOLD stage 1).[4,31,43]
- **Smoking status:** Current smoking may affect azithromycin efficacy.[31] Important to evaluate, NICE recommend only in non-smokers specifically, BTS recommend smoking cessation optimisation prior to starting treatment.[1,2]
- **CAT score (symptom burden/impact):** NICE recommend evaluation of prognostic factors in COPD care because of potential therapy implications.[1] Of prognostic factors, CAT score is likely most useful to evaluate.
- **Blood eosinophil counts:** Evidence suggests both low or high counts may be a marker of treatment responsiveness to azithromycin.[32, 33] GOLD recommend azithromycin in low eosinophils, frequent exacerbators (expert opinion).[3] Eosinophilia is an uncommon side effect of azithromycin.[44] This exploratory subgroup analysis will evaluate highest and lowest blood eosinophil count in approximately last 3 years and eosinophil count as a baseline trial assessment if it is feasible to do this.
- **Age:** Older age associated with greater treatment efficacy in one post-hoc analysis,[31, 32] although not in another. Important to evaluate azithromycin effectiveness as well as side effects/risks.
- **Azithromycin baseline prescription:** Whether a participant's baseline azithromycin prescription dosing impacts trial's endpoints.

Of interest/exploratory:

Undertaking these exploratory analyses will be dependent on whether there are sufficient numbers in subgroup stratification to do so.

- **Diagnostic phenotype:** Chronic bronchitis will be defined by a baseline questionnaire. Whether a participant has emphysema, bronchiectasis and/or small airway disease may be known and recorded based on medical records or self-reported. If a participant has had a CT, the summary report may be reviewed as a data source. Whether sufficient data on this diagnostic phenotype can be obtained to enable subgroup analysis is unknown and will be reviewed whether appropriate to evaluate or not.
- **Demographics: Sex:** Important to evaluate if effectiveness and side effects vary by sex.

- **Positive sputum culture of bacteria and mycobacteria in last 12 months prior to enrolment (i.e. baseline status):** Including specific analysis of *Pseudomonas aeruginosa* positive culture. Observational evidence suggests *Pseudomonas aeruginosa* positive culture may be marker of treatment responsiveness in COPD.[34]
- **Inhaled corticosteroid use:** Inhaled respiratory therapy and oral prednisolone appear not to impact on azithromycin efficacy in two previous trials.[31,44] However, these trial populations were not representative of regular treatment regimens real-world COPD patients prescribed azithromycin may be on.

15.2 Interim Analyses

Interim analyses are scheduled for approximately 18 months after the first participant is enrolled but may be later in the trial depending on recruitment and number of events (i.e. exacerbations). The choice is flexible and only has a minor impact on the expected number of events over a range of hazard ratios. The total number of observed events across 3 arms is expected to be around 350 at 18 months, with around 700 recruited; the interim analyses may be rescheduled if the number of events or recruits is substantially out from these predictions. These analyses will inform a recommendation to drop a treatment arm on the basis of futility made by the trial's DMC (the standard care arm will always be continued). This decision will be informed by Bayesian posterior distributions for the treatment effects on the primary outcome of each experimental treatment. Based on a vague prior distribution with 95% weight between hazard ratio of 0.5–2.0, an early stopping guideline would be if a posterior distribution gave more than 70% probability to a hazard ratio higher than 1.25.

15.3 Participant Numbers

This is an event-driven, non-inferiority trial, where the sample size and duration of follow-up is dependent on the number of primary endpoint (time to first exacerbation) events that occur. Estimation of the number of events required and therefore modelling of sample size required to achieve this number of events is based on available evidence.

Assuming a median time to first exacerbation (TTFE) of 150 days[4,9,43] in the control standard of care arm (continuous treatment), and a non-inferiority threshold of 30 days, equates to the threshold on the hazard ratio scale of 1.25. The non-inferiority threshold of 30 days selected, was judged by respiratory specialists to be a clinically relevant margin of TTFE. There are no validated minimum clinically important differences for COPD exacerbations, including time free or until a COPD exacerbation. Given that a 2-week window between exacerbations is often used to define separate events,[46] TTFEs reviewed in azithromycin trials,[4,9,43] as well as TTFE in a large non-inferiority COPD treatment trial (FLAME trial),[64] all support 30 days as a reasonable non-inferiority margin.

Sample size is based on 90% power for two non-inferiority comparisons (seasonal and placebo compared with continuous as standard treatment), at 2.7% significance (Dunnett test for multiple comparisons) using a Cox proportional hazards model. The number of primary endpoints required is **1242**. We assume a recruitment rate of ~560-630 participants per year,[48,50] and a recruitment period of 29 months.

The total **sample size** estimate is thus **1311 (n=437 per arm)** and allows for ~5% dropout before the primary endpoint (first exacerbation), or censoring, to achieve the required 1242 events.

Data from previous withdrawal trials of corticosteroids[65,66] suggest that adverse events (COPD exacerbations predominantly) was the main reason for dropouts. Given that our primary endpoint is TTFE, and that the expected median time to the primary event is approximately 5 months, only a tiny number of dropouts should happen before the primary event occurs. The anticipated median follow-up period of 24 months for the trial cohort is

nearly 5 times as long as the median event time (5 months), hence the proportion of censored patients who do not observe an event by the end of follow-up will be small. This important assumption for dropout rate will be considered at the interim analyses. Potentially a reduced total sample size would be used, with a generous adjustment for dropouts, should an arm be dropped for futility. Final analysis will occur once the target number of events have occurred, or as advised by the TSC based on input from the DMC, whether the trial should continue for secondary endpoints accrual.

15.3.1 Sample size and Duration of Follow-up Sensitivity

The primary endpoint event rate will be monitored using data blinded with respect to treatment arm assignment. If the event rate is lower than anticipated, then the TSC in discussion with the NIHR will decide whether to increase the sample size or whether an increased duration of follow-up is acceptable. We anticipate based on assumptions stated above, that a median duration of follow-up of approximately 24 months is needed to reach our target number of events. However, the possibility of a longer follow-up if needed, may be considered; since flexibility for duration of follow-up is anticipated and planned for accrual of secondary endpoints, if appropriate. An increase in sample size if required, will be most practically implemented prior to the end of the recruitment period. If the recruitment has closed already, then the trial follow-up duration may need to be extended. As an event driven trial, the recruitment period length will also impact the number of participants and/or duration of follow-up required. For example, if the recruitment rate is slow, and the event rate high, the required number of events may have occurred before 437 subjects/arm are randomised. The current recruitment period estimated for the trial is 29 months, with anticipated plans for the trial to run for follow-up of approximately 24 months after. Therefore, if the recruitment rate is slower than anticipated, given that the length of follow-up to estimated time to event is assumed to be relatively longer, then the TSC in discussion with the NIHR can review whether it is appropriate to extend the recruitment period, to reach a sample size necessary for number of events.

The trial design has been set up for a long period of follow-up relative to assumed time to primary events, to enable evaluation of the secondary endpoints of the trial. Although the trial is not powered for secondary endpoints, to accrue data regarding hospitalisations and mortality in this cohort, not only on the trial IMP but also back on their regular azithromycin prescription, is considered *a priori* an important aim of the trial. There is a lack of data on hospitalisation and mortality rates in this population (people with COPD on long term azithromycin). Given that there has been no trial evaluating complete or seasonal discontinuation of antibiotic prophylaxis in COPD, it is desirable to ensure that the trial does not stop before sufficient information is gathered to provide a definitive result. However, it is recognised that there may be reasons for stopping the trial earlier than anticipated, for example due to overwhelming evidence of efficacy or safety, or if the target number of events have occurred and it is considered not appropriate to continue the trial for secondary endpoints accrual. Data from the IDMC and advice and recommendations from the TSC will determine this.

For these reasons, one formal interim analysis is planned as described in section 15.2.

15.4 Guidelines for the Premature Termination of the Trial

Guidelines for the premature termination of the trial are summarised below. However, advice and recommendations from the TSC based on information from the IDMC and with input from the NIHR may consider premature termination of the trial for other reasons besides those considered below.

- **If both experimental treatment arms are futile at the interim analysis.**
- **Safety reasons. The IDMC will review blinded data periodically.**
- **Following guidance from the IDMC, TSC and also NIHR, if it is unfeasible to continue the trial.**

15.5 Procedure to account for Missing or Spurious Data

The primary endpoint is a time-to-event endpoint. If a participant withdraws fully or completes full follow-up, before experiencing their first exacerbation then their observation is treated as a censoring.

Secondary and exploratory endpoints may be still observed even if a participant withdraws from protocolised treatment, and thus will be analysed. The proportion of missing values will be reported, and a default analysis will be based on complete cases, thus assuming Missing Completely At Random. Further sensitivity analyses will be detailed in a SAP.

15.6 Economic Evaluation

In order to estimate which of the three treatment regimes ((i) total discontinuation, ii) seasonal discontinuation, and iii) continuing azithromycin) is most cost-effective, an economic evaluation will be undertaken.

In line with the National Institute for Health and Clinical Excellence (NICE) technology evaluations manual[67], costs will be estimated from an NHS perspective. Specifically, intervention costs (for each of the three treatment options) will be estimated from trial treatment data (dose, frequency of administration, etc.) along with COPD related costs for hospital admissions, primary care consultations and medication data.

The main measure of effect in the economic analysis will be the EQ-5D-5L (patient self-report data requested at baseline and follow-up trial visits), as this will enable quality adjusted life year (QALY) scores to be estimated.

A Health Economic Analysis Plan (HEAP) will be developed prior to analysis. This will detail the methods to be used to estimate the incremental cost and effect (QALY gain) associated with i) total discontinuation and ii) seasonal discontinuation, both compared to continuing azithromycin. For each discontinuation option, net benefit will be estimated at a threshold value e.g. £20,000 per QALY, where a positive value would indicate discontinuation was estimated to be cost-effective. The associated level of uncertainty will also be estimated.

15.7 Definition of the End of the Trial

The end of the trial will be the date of the last patient's last visit (LPLV).

16 DATA HANDLING AND RECORD KEEPING

16.1 CRF

All data will be transferred into a Case Report Form (CRF) which will be de-identified. All trial data in the CRF must be extracted from and be consistent with the relevant source documents.

Electronic case report forms (eCRFs) will be used to collect the data, all data will be entered onto a secure electronic database. The database, which will be MHRA and GDPR compliant, will be secured by appropriate access control and password protection. All trial data in the eCRF must be extracted from and be consistent with the relevant source documents. The eCRFs must be completed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness and accuracy of the eCRF. The eCRF will be accessible to trial coordinators, data managers, the investigators, Clinical Trial Monitors, Auditors and Inspectors as required. In the situation where the database is down or there are other problems that mean eCRFs cannot be used, the data will be recorded on paper CRFs as a back-up.

Data provided to the central coordinating team will be checked for errors, inconsistencies, and omissions. If missing or questionable data are identified, the central coordinating team will request that the data be clarified.

16.2 Source Data

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating participants (sufficient information to link records e.g. CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

Source data are:

- Medical records
- Signed Informed Consent forms
- Online test result systems
- Participant diaries for COPD flare-ups
- Questionnaire pack
- NHS digital data
- Reported SAE forms

16.3 Data Protection & Participant Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 2018 and Trust Policy with regards to the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

Trial participants will provide explicit consent to the use of identifiable data for the purposes of the conduct of the trial.

Patient identifiable data (PID) will be accessible to limited GCP-trained members of the trial team including central pharmacy to enable dispensing of trial medication (information required for this: name and contact details: home address and postcode, telephone number and email address where applicable to facilitate dispense and courier of trial medication). A limited number of GCP-trained members of the OPACE trial management team within the Cambridge Clinical Trials Unit, may need to access PID (name, date of birth, gender, NHS number or equivalent, home address and postcode, telephone number and email address) where applicable as required for trial purposes. It is necessary to 1) perform linkage to national datasets (NHS Digital and equivalent in devolved administrations and 2) if needed to aid central pharmacy coordination of home delivery of trial medication. Sponsor monitors, auditors and inspectors may need to access PID data as part of their process of trial monitoring.

All PID downloaded from NHS Digital and the equivalent national health record organisations will be stored securely on the University of Cambridge, School of Clinical Medicine Secure Data Hosting Service (SDHS). The SDHS is registered and approved under the NHS Digital Data Security and Protection Toolkit and is ISO 27001 certified.

17 DATA MONITORING COMMITTEE/TRIAL STEERING COMMITTEE

Data Monitoring Committee

The ethical and safety aspects of the trial will be overseen by an independent DMC. IDMC meetings will be timed so that reports can be fed into the TSC meetings. Full details of the IDMC membership and remit can be found in the IDMC Charter. Minutes will be taken at these meetings, which will be signed by the Chair of the Committee.

Trial Steering Committee

The TSC provides overall supervision for the trial on behalf of the Sponsor and Funder (NIHR), to ensure that it is conducted in accordance with the protocol and GCP and to

provide advice through its independent chairman. The committee will aim to convene at regular intervals to review the data and discuss the progress of the trial at a top level, including adherence to the protocol, participant safety and considerations for new information, specified in the TSC charter. Full details of the TSC membership and remit can be found in the TSC charter. Minutes will be taken at these meetings, which will be signed by the Chair of the Committee.

Trial Management Group

The trial project management group (TMG)'s role is to oversee the day to day running of the trial, data management and monitoring. It will be set up and follow the terms and conditions as per a CTIMP charter template for a trial management group. It is made up of the CI(s) and other grant holders as appropriate, the trial coordinator and other senior members of the Cambridge Clinical Trials Unit (CCTU) and other members of the respiratory/trials community that will provide advice and collaboration to enable facilitation of the trial. TMG meetings will take place on a weekly basis to discuss progress of the trial and any issues that require resolving. Minutes will be taken at these meetings.

18 ETHICAL & REGULATORY CONSIDERATIONS

18.1 Ethical Committee Review

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the CI's responsibility to produce the annual reports as required.

18.2 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Development Safety Update Reports (DSURs) will be submitted to the MHRA in accordance with national requirements. It is the CI's responsibility to produce the annual reports as required.

18.3 Heath Research Authority (HRA)

HRA approval is required for all UK trials prior to commencement.

18.4 Protocol Amendments

Protocol amendments must be reviewed and agreement received from The Sponsor for all proposed amendments prior to submission to the HRA, REC and/or MHRA.

The only circumstance in which an amendment may be initiated prior to HRA, REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the HRA, REC and/or MHRA approval has been obtained.

18.5 Peer Review

This trial has undergone extensive internal and external peer review as part of the funding process, the protocol has been subject to internal peer review and is approved by the Sponsor.

The trial proposal has been through the NIHR peer review process as a requirement of the HTA award. The trial project documents have undergone internal and external peer review including by a patient panel and is approved by the Sponsor.

18.6 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

18.7 GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust's policy.

19 SPONSORSHIP, FINANCIAL AND INSURANCE

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and University of Cambridge. The trial will be funded by the NIHR Health Technology Assessment Programme (134464).

The funder National Institute for Health Research, Health Technology Assessment has oversight of the trial through regular reports from the trial office. The funder appoints the independent members of the Data Monitoring and Trial Steering Committees and receives minutes from their committee meetings. The funder is made aware of all outputs from the trial and will be sent these prior to publication but does not have a role in the decision to publish results from the trial. In any publications, the funder is acknowledged, and appropriate disclaimer used to indicate that the views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

Participant Expenses

Participants will be reimbursed for their travel expenses (car parking, fuel, bus, train tickets) for participating in the trial in certain circumstances. The Participant Information Sheet and a separate participant expenses policy will explain procedures for reimbursement.

20 MONITORING, AUDIT & INSPECTION

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to The Sponsor's representative. All participant data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

Monitoring of participating sites will occur in line with the trial specific monitoring plan.

21 PROTOCOL COMPLIANCE AND BREACHES OF GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the CI and The Sponsor immediately.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to The Sponsor without any delay.

22 VENDORS / CONTRACTORS

22.1 External Vendor / Contractors

Sealed Envelope will be used to randomise participants, as well as allow emergency unblinding.

Eramol (UK) Limited will be used for supply and storage of IMP.

WGK Clinical Services will act as the central pharmacy. They will receive and store IMP stock from Eramol, dispense, provide accountability, and distribute blinded IMP directly to the recruited participants via their designated courier services.
Red Graphic will design the OPACE trial website.

22.2 Central Facilities

See Section 22.1 above.

23 PUBLICATIONS POLICY

Ownership of the data arising from this trial resides with the trial team. On completion of the trial the data will be analysed and tabulated and a Final Trial Report prepared.

Any reported serious breaches will be detailed in all publications in line with regulatory requirements. The Sponsor will review any publications prior to submission. The NIHR will review and provide approval for any publications prior to submission and funding (NIHR), support. A separate authorship policy will be produced and will be in accordance with ICMJE guidelines.

24 DATA TRANSPARENCY

24.1 Informing Participants of the Results of the Trial

Participants in the trial will be provided with a specifically designed newsletter explaining the trial results and what they mean and potential impact of them.

24.2 Informing sites of Trial progress

Newsletters will be produced on a quarterly basis to inform sites of trial progress.

25 DATA AND SAMPLE SHARING

A separate data sharing policy with appropriate safeguards will be established and in keeping with the policies of the Sponsor and funder. No research biological samples are taken in the main OPACE trial for storage or sample sharing. Any samples or data taken for any associated ancillary study will be covered by a separate protocol and ethics submission.

26 ARCHIVING

As per current regulations, once the trial has come to an end and the analysis has been reported to the regulatory authorities, essential trial documentation as part of the TMF will be archived in keeping with The Sponsor’s policy and applicable regulations for a period of 5 years.

All trial related documentation and data as part of the investigator site file will be archived in accordance with participating site's standard operating procedures and The Sponsor's timelines. These procedures state suitable locations to be specified at the time of archiving with limited access to named members of the research team only.

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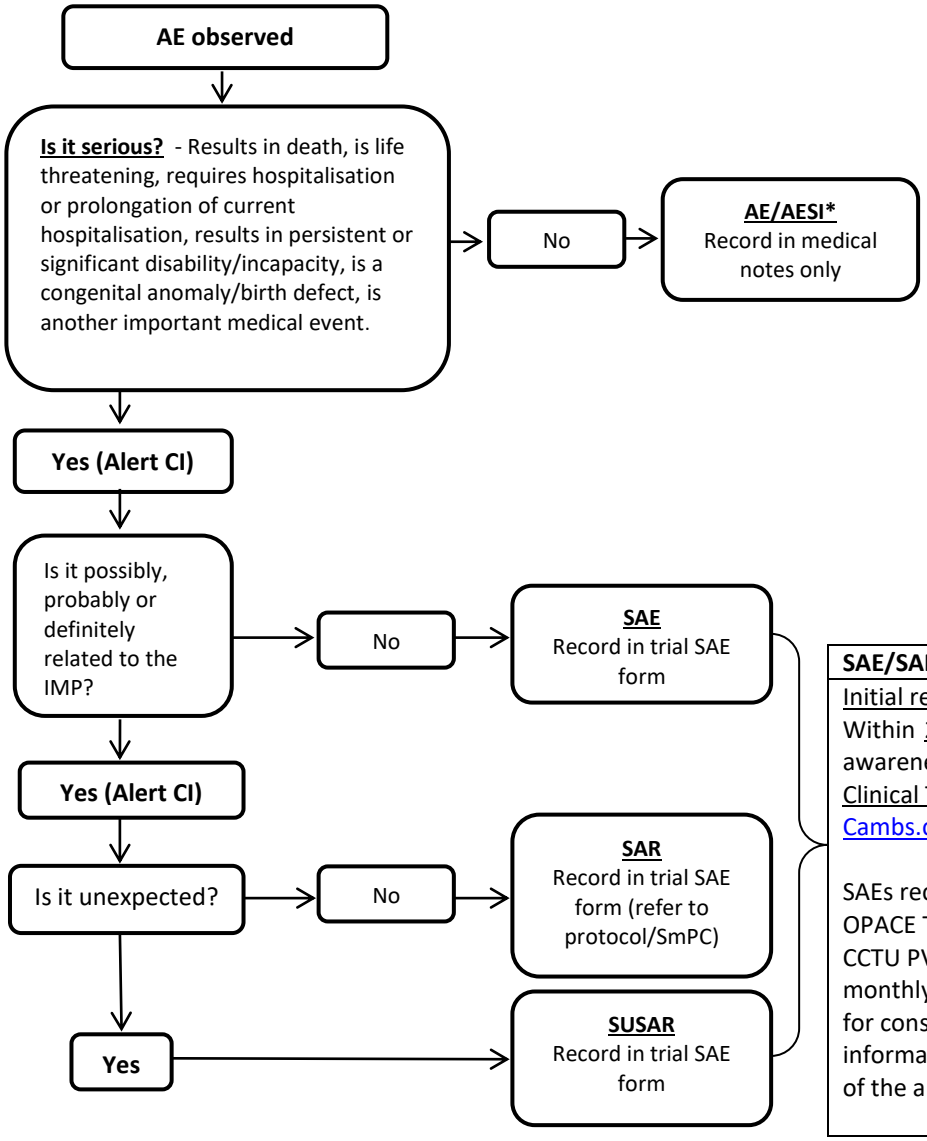
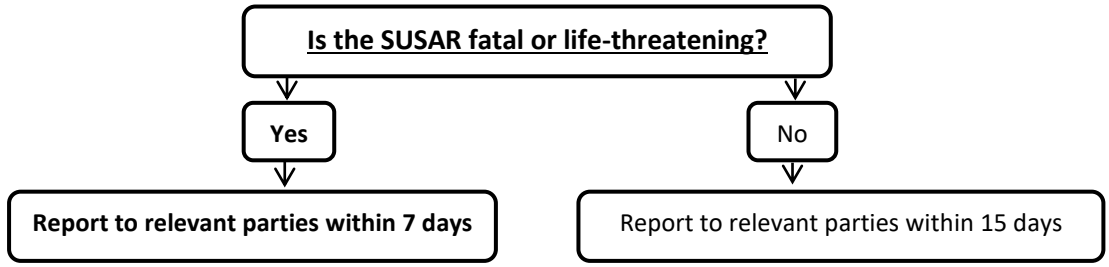
28 SAFETY REPORTING FLOW CHART



SUSAR expedited reporting

The Chief Investigator must report a SUSAR to the relevant parties (Sponsor, REC and MHRA) within statutory timelines. Each SUSAR requires the entry of relevant data and information by the Chief Investigator into the SUSAR reporting system (ICSR). A copy of this report should be provided to the CCTU PV team, collating these on behalf of the sponsor.



*AESI will also be recorded in the AESI form

29 APPENDIX A: Study within a trial (SWAT)

Evaluation of the impact of text message invite in a pragmatic trial in people with COPD, on participant response and recruitment.
(Funder: NIHR)

Background:
Text message (SMS) communication with patients regarding appointments, reminders, and prescriptions for example, is now a routine communication method used in the NHS, both in primary and secondary care. More recently, text message invites were employed in UK nationally important large COVID trials such Panoramic and Principle and sent to potential participants identified as COVID-19 positive from laboratory testing.[1,2] The individual impact of this intervention in these trials and generalisability to other clinical trials research in the UK is uncertain, given the unique and urgent situation of the pandemic and therefore imperative need of research in this context, and the fact a number of other different methods to try and maximise participant involvement as much as possible were used in conjunction in these trials.

A literature search (PubMed) retrieved no results for combinations of "SMS invites clinical trials, text invites clinical trials, text message trial recruitment". Text message as an intervention *itself* has been evaluated in a few trials (smoking cessation, weight loss, cervical screening) but not specifically evaluated as a tool to potentially improve participant response and recruitment.[3,4,5]

People living with COPD, are elderly, and live with significant health and socioeconomic inequalities. Given that areas with high COPD prevalence are often under-represented in clinical research and it is a strategic aim of health research in the UK to improve representation of under-served groups, it would be helpful to assess the intervention of text message invites in a trial outside of COVID, in a condition with relatively high disease prevalence, and with demographic characteristics typical of frequent healthcare users in the UK. Whether they are a cohort that would respond well to a text message invite is unknown, since they are more elderly and perhaps less technology literature than the cohorts of participants recruited to COVID trials. A review of SWAT studies on the Queens University portal identifies 11 studies where SMS have been evaluated in some form, although no study thus far has looked at the effectiveness of this simple intervention on interest and recruitment in trials.[6]

Aim: To determine the impact of text message invite to the OPACE COPD trial on participant recruitment.

Methods:
Healthcare sites that are willing and able to participate in this SWAT within the OPACE trial, will identify eligible participants by screening and send out a text invitation in addition to regular participant invite materials vs no text invite and regular participant invite materials. Text invite will be a standard REC approved text. This will be an additional recruitment tool used in addition to routine participant invite materials.

Statistical analysis:
Simple summary statistics will be used to collate and describe data.

The number of eligible participants identified by screening at a site and sent participant invite materials (+/- SMS) will be recorded. It is anticipated that the SWAT will run for approximately 1 year to enable sufficient recruitment to undertake statistical analysis if this is feasible.

A formal analysis plan for the SWAT will be developed and approved by the trial statistician prior to analysis.

The SWAT is planned to be active within the OPACE trial. If unexpected challenges in implementation of SWAT arise this does not affect the main trial.

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30 APPENDIX B: Study within a project (SWAP)

To better understand frailty in people living with COPD, a population with multimorbidity.
(Funder: NIHR)

Background:
People living with COPD are often frail and have significant comorbidities, such as cardiovascular disease, diabetes, anxiety, osteoporosis and lung cancer.[1,2] They are a population living with multimorbidity (that is ≥2 long-term conditions as per NICE definition[3]) and their frailty and comorbidities (co-existing conditions to their COPD) likely adversely impact outcomes such as all-cause mortality, and clinical care decision-making. COPD is one of 5 long-term conditions (other 4: multiple sclerosis, diabetes, connective tissue disease and diabetes) associated with frailty in a UK Biobank multimorbidity and frailty analysis of nearly ~500,000 participants.[4] NICE recommend that frailty is screened for in people with multimorbidity.[3]

However, there is a lack of research on simple, easy-to-use, clinically relevant frailty assessments in people living with COPD. The self-rated health scale (SHS), one of NICE's recommended frailty screening tools, is easy to do anywhere, patient-reported and is only 1 question-long (*'how would you rate your health status on a scale from 0 to 10?', with scores ≤6 indicating frailty)*. Nevertheless, its association with frailty and utility in risk prediction of adverse outcomes in people living with COPD has not been tested before. Moreover, frailty defined by measures such as the Rockwood Clinical Frailty Scale (CFS) and electronic Frailty Index (eFI) which are recommended tools routinely used in clinical practice and their association with adverse outcomes in COPD are also unknown.[5,6,7] Furthermore, the utility of the Cambridge multimorbidity score which has been shown to predict key health outcomes of mortality, unplanned hospital admissions and primary care consultations[8] will be assessed and possibly explored in context with the frailty parameters evaluated in this SWAP.

Aim: To better understand frailty in people living with COPD, a population with multimorbidity.

Objectives:
1) Is SHS a useful surrogate measure of frailty in COPD patients?
2) Does SHS (and CFS and eFI) have value in risk stratification of COPD patients for adverse outcomes?
3) To describe the trajectory of frailty in COPD patients.
4) Evaluation of the Cambridge Multimorbidity score in COPD patients.

SWAP design
Utilising data collected as part of the main trial and outcome data from NHS Digital and similar services in devolved administrations, will enable evaluate utility of simple frailty screens in risk stratification for outcomes (hospital admissions and mortality). Repeat assessment of frailty at end of trial will enable assessment of frailty trajectory. Routinely collected data can be used to assess the Cambridge multimorbidity score in patients.[8]

Study population
The OPACE COPD trial population with multimorbidity. It is anticipated most participants will have multimorbidity (NICE definition ≥2 long-term conditions and would be inclusive of their COPD) based on prevalence of 51-96% of COPD patients having ≥1 co-existing condition from epidemiological studies. IF the proportion with/without multimorbidity by this definition means analysis stratified by multimorbidity (presence of vs not, and multimorbidity severity) is of merit we will also explore analysis by this stratification.

Study size
The size of the OPACE trial population with multimorbidity.

Inclusion criteria:
Same as for OPACE trial (see sections 8.1 and 8.2 of the core Protocol) and multimorbidity (defined as per NICE: ≥2 long-term conditions and would be inclusive of their COPD).

As mentioned earlier if the proportion of participants without multimorbidity is sufficient (~5%) to undertake analysis stratified by presence/or not of multimorbidity, this will be undertaken.

Study assessments:
The study assessments are integrated into the main trial, i.e. the SHS at baseline and end of trial. All other data required to answer this SWAP's objectives is collected/recorded as part of the trial. Data from NHS digital (and similar services) will be used for hospital admissions data.

Statistical analysis
Given the exploratory nature of this SWAT in a trial population size powered by the trial's primary outcome, we feel a formal sample size calculation is inappropriate. However, the trial's cohort size is similar to epidemiological studies to evaluate these observations and has longitudinal follow-up. Associations of SHS with frailty defined by CFS and eFI will be evaluated by regression models with inclusion of important covariates. Cox regression models will be used to assess the predictive value of SHS, CFS and eFI of hospitalisations, length of stay and mortality. Whether these frailty measures perform differently in men and women with COPD will also be explored. Lastly, the change in SHS, CFS and eFI over time in the trial cohort will be described and evaluated using linear mixed models. Cambridge multimorbidity score will also be calculated at baseline and follow-up and its association with frailty parameters may be explored.

Potential Results/Outcome
This will be the first study to evaluate the utility of SHS as a proxy tool for frailty in COPD, utility of frailty measures to predict adverse outcomes and the trajectory of clinically important frailty measures in a reasonable sized COPD multimorbid cohort.

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