Academic and Clinical Central Office for Research and Development

Study Protocol

What is the clinical effectiveness and cost-effectiveness of nebulised 7% sodium chloride in patients with chronic obstructive pulmonary disease?

(MucAct COPD Study)

Co-sponsors	The University of Edinburgh & Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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PROTOCOL APPROVAL SIGNATURE PAGE

What is the clinical effectiveness and cost-effectiveness of nebulised 7% sodium chloride in patients with chronic obstructive pulmonary disease?

(MucAct COPD Study)

EudraCT 2020-001949-39

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Prof Adam Hill		
Chief Investigator	**Signature**	**Date**
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For multi-site trials, the **Principal Investigator** must sign below to document that the protocol has been read and understood.

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LIST OF ABBREVIATIONS

ACBT	Active Cycle Breathing Technique
ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
BLF	British Lung Foundation
BNF	British National Formula
CAT	COPD Assessment Test
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
ECTU	Edinburgh Clinical Trials Unit
EudraCT	European Clinical Trials Database
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCRU	Health Care Resource Use
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product

ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LCQ	Leicester Cough Questionnaire
MRC	Medical Research Council
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient & Public Involvement
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
QA	Quality Assurance
QALY	Quality Adjusted Life Years
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SGRQ	St. George's Respiratory Questionnaire
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
URTI	Upper Respiratory Tract Infection
VoI	Value of Information

WURSS-24 Wisconsin Upper Respiratory Symptom Survey 24

TRIAL SUMMARY

Trial Title	What is the clinical effectiveness and cost-effectiveness of nebulised 7% sodium chloride in patients with chronic obstructive pulmonary disease (COPD)?
Study Acronym	MucAct COPD Trial
Clinical Phase	Phase III
Trial Design	Open pragmatic UK multi-centre parallel randomised controlled trial with process evaluation and health economic analysis.
Trial Participants	Participants with COPD that have either chronic bronchitis and/ or associated bronchiectasis that have self-reported difficulty self-expectorating
Planned Number of Participants	860
Planned Number of Sites	10-20
Countries Anticipated to be Involved in Trial	UK
Treatment Duration	1 year
Follow up Duration	1 year
Total Planned Trial Duration	53 months
Primary Objective	Assess whether nebulised 7% sodium chloride plus Active Cycle Breathing Technique (ACBT) is superior compared with carbocisteine plus ACBT when comparing the change in COPD Assessment Tests (CAT) over one year period (+/- 21 days).

Secondary Objectives	Over a one year period (+/- 21 days), to assess whether nebulised 7% sodium chloride plus Active Cycle Breathing Technique (ACBT) is superior compared with carbocisteine plus ACBT when comparing: 1. health related quality of life; 2. reducing exacerbations and prolonging the time to first exacerbation; 3. reduction of potential pathogen microorganisms from sputum samples and viruses from combined nose and throat swabs (latter if taken as part of standard care); 4. viral transmissibility 5. stabilise or improve lung function; 6. health economic benefits. 7. adverse effects, 8. adherence in both arms of the study.
Primary Endpoint	Assess whether nebulised 7% sodium chloride over one year (+/- 21 days) with ACBT airways clearance is superior compared with oral carbocisteine with ACBT over one year in leading to a 2 Unit or greater increase in the COPD Assessment Test (CAT).

Secondary Endpoints	Assess whether nebulised 7% sodium chloride with ACBT is superior compared with oral carbocisteine with ACBT in leading to: • Health related quality of life; • An improved CAT score at 6 months compared with baseline; • An improved quality of life assessment using the Leicester Cough Questionnaire and St. George's Respiratory Questionnaire at 6 months and 1 year. We will assess the mean change from baseline to 6 months and baseline to one year between total LCQ scores between groups but also compare the number that have a 1.3 unit or more improvement in total LCQ scores between groups; • Reducing exacerbations and prolonging the time to first exacerbation; • A reduced number of exacerbations over a one year period requiring antibiotic therapy and/or systemic steroid treatment; • A prolonged time to first exacerbation requiring antibiotic therapy and/or systemic steroids over one year • A reduced proportion of exacerbations needing antibiotic therapy over one year • A reduced number of upper respiratory tract infections (URTI) over a one year period) assessed using the Wisconsin Upper Respiratory Symptom Survey-24 (WURSS-24) • A reduced overall and COPD related hospital attendances/admissions over one year • Frequency of use of nebulised 7% sodium chloride in exacerbations. • Reduction of potential pathogen microorganisms from sputum samples and viruses from combined nose and throat swabs (latter if taken as part of standard care); • A reduced proportion being infected with a potential pathogenic organism and viruses at 6 months and one year (from sputum samples and combined nose and throat swabs)

	• Stabilise or improve lung function; • Stable or improved Forced Expired Volume in 1 second (FEV1), Forced Expired Volume in 6 seconds (FEV6) and mid-expiratory flows at 6 months and one year • Viral transmissibility in household contacts • Health economic benefits; • Cost per Quality Adjusted Life Year (QALY) a) over one year and b) modelled over a lifetime horizon • Compare adverse effects; In addition, we will compare nebulised 7% sodium chloride and ACBT with oral carbocisteine and ACBT in: • Adverse events over one year; • Adherence with interventions assessed by weekly participant charts and enquired at study appointments over one year.
IMP(s)	Nebulised 7% sodium chloride and 750mg carbocisteine
IMP Route of Administration	Nebulised 7% sodium chloride and oral carbocisteine
NIMP(s)	Salbutamol

Lay Summary

Aim(s) of the research

We want to study whether breathing in salty water through a nebuliser can help patients with Chronic Obstructive Pulmonary Disease (COPD) cough up phlegm, make them feel better and cut down the number of chest infections they have. We also would like to know whether this is better than taking capsules (carbocisteine), also thought to help patients clear phlegm from the airways.

A nebuliser is a machine that creates a mist, which can be inhaled through a mask or tube. The salty water can be inhaled through a nebuliser to help clear excess mucus from the airways. There is poor evidence of what treatments help clear mucus from the airways. Usually carbocisteine tablets are used (to help clear mucus from the airways). The study investigators believe inhaling salty water is better at clearing mucus from the airways and has additional beneficial effects combating bacterial and viral infection.

Background

Some patients with COPD find it hard to clear sputum (phlegm) from the airways. Unfortunately, there's no good evidence that shows the best treatment for patients.

How we will do the study

We will recruit 860 patients with COPD throughout the UK.

Half of the group, at random, will inhale salty water through a nebuliser twice a day for 1 year. The other half will get carbocisteine capsules daily for 1 year. It is not possible for it to be a blind trial because the participants and clinician will obviously know the treatment given. Both groups will be taught chest clearance using a video of breathing and coughing techniques that they can use twice a day to help clear phlegm from the chest.

The main goal of the study is to see whether inhaled sodium chloride is better and is more cost effective than oral carbocisteine which is the traditional medication used. Theoretically, inhaled sodium chloride is better than carbocisteine at clearing phlegm in the airways.

Ethics and data protection

The study will only begin following approvals of the multi-centre research ethics committee, approval by the Medicines and Healthcare products Regulatory Agency (MHRA) and management approval.

Data protection will comply with relevant data protection regulations.

Involving patients and the public

Our grant proposal has been reviewed by the Asthma UK and British Lung Foundation (BLF) Partnership, University of Edinburgh Patient & Public Involvement (PPI) group based in the Usher Institute and the patient group "Breathtakers, Action for Bronchiectasis". We amended our plans for the study after getting their feedback. The PPI group also helped with writing this lay summary. A member of the PPI group has now joined as a co-applicant and two separate members will join the steering committee for the trial who will link to the Asthma UK and BLF Partnership patient advisory group.

Who will hear about the results

We will present our findings at local, national and international meetings. The University of Edinburgh PPI group and the Asthma UK and BLF Partnership have also offered to help spread the word. This study won't just help the National Health Service (NHS) but could also be applied internationally - so we aim to publish the paper in an influential and widely read medical journal.

1. INTRODUCTION

1.1 BACKGROUND

Chronic cough is a prominent symptom in COPD and is often accompanied by increased sputum production [1]. It is associated with fatigue, reduced ability to perform activities of daily living and reduced quality of life [1]. Some patients struggle to expectorate sputum and may benefit from measures to support airway clearance and expectoration.
Oral muco-active drugs are often prescribed (the most common being carbocisteine), but may not be suitable for all patients due to side-effects, contra-indication or preference [1].
Nebulised hypertonic sodium chloride has been shown to be an effective alternative muco-active treatment in patients with cystic fibrosis [3], but no large randomised controlled trials (RCT) have been carried out in patients with COPD [1].

Current use of sodium chloride and carbocisteine in practice

From analysis of the Clinical Practice Research Datalink (courtesy of Senior Data Analyst, Mukherjee), there were 4,623 patients with COPD on Dec 17-Nov 18. Carbocisteine was prescribed in 9.0% of mild COPD patients, in 11.4% of moderate COPD patients, in 26.3% of severe COPD patients and in 39.4% of very severe COPD patients. Sodium chloride was prescribed (dose not known) in 1.9% of mild COPD patients, in 2.4% of moderate COPD patients, in 6.2% of severe COPD patients and in 7.4% of very severe COPD patients. Thus, in routine care, carbocisteine is the main muco-active agent used and its use increases with COPD disease severity.

A systematic review evaluated the effectiveness of oral carbocisteine (500mg three times daily) compared with placebo for six months to one year [4]. There were four trials involving 1,357 patients. There was a decrease in the number of exacerbations per person per year with carbocisteine compared with placebo (-0.43; 95% confidence interval [CI] -0.57 to -0.29,
P<0.01) and a reduced number of patients with at least one exacerbation (0.86; 95% CI 0.78 to 0.95) compared with placebo. There was no significant difference in the Forced Expired
Volume in 1 second (FEV_1), in adverse effects or in the rate of hospitalisation.

There are no systematic reviews investigating the effects of nebulised sodium chloride in COPD [1].
There was only one small RCT evaluating the effect during an acute exacerbation, but there are no long-term efficacy studies [5]. In this trial, 40 patients were studied following hospital admission with an exacerbation of COPD (mean FEV_1 30% predicted) and randomised to single-blind administration of either 4 mls of nebulised 0.9% sodium chloride using an efficient nebuliser (intervention group n = 20) or an inefficient nebuliser (placebo group n = 20). Spirometry and subjective breathlessness scores

(Modified Likert Scale) were measured before nebulised treatment and 10 minutes after treatment. There was no significant change in FEV_1 after active or placebo nebulised 0.9% sodium chloride treatment. Patients reported a 4% improvement in mean breathlessness score following placebo (Wilcoxon test; p = 0.37) compared with 23% improvement following active nebulised sodium chloride (p = 0.0001).65% of patients were given active nebulised 0.9% sodium chloride but only 5% of the placebo group reported that mucus expectoration was easier after the treatment.

In addition to aiding sputum clearance, there is preliminary evidence that hypertonic sodium chloride has both antibacterial and antiviral benefits. Most exacerbations of COPD are preceded by an infection. Ramalingam S et al have shown that human epithelial cells utilise sodium chloride to mount a broad-spectrum antiviral effect against DNA, RNA, enveloped and non-enveloped viruses [6]. The antiviral effect is dependent on the entry of chloride (not sodium) ions into the cell. The laboratory evidence is supported by the results of a pilot RCT of hypertonic sodium chloride nasal irrigation and gargling for the common cold in adults which showed a significant reduction in duration of illness by two days, viral shedding, transmission within the household and over the counter medication use [7]. Jantsch et al have reported that accumulation of Na+ ions in human skin helps fight bacterial/parasitic infections [8]. Taken together, these data suggest that innate immunity may be dependent on sodium chloride (NaCl) in epithelial cells helping to clear bacterial and viral infection.

The recent evidence of antiviral and antibacterial effects of sodium chloride emphasises the need for a control arm which does not have sodium chloride (i.e. sodium chloride) which traditionally has been used as a placebo for studies of hypertonic sodium chloride [9]. Over 12 weeks, although there was no significant difference in quality of life between arms, the hypertonic sodium chloride arm had a significantly better health perception scale in the Quality of life Questionnaire–Bronchiectasis [29]. Compared with no treatment, the antiviral and antibacterial effects of sodium chloride will have a larger role to play in reducing exacerbations if the duration of follow up is longer than 12 weeks as was the case in cystic fibrosis patients who either received nebulised 7% sodium chloride or 0.9% sodium chloride twice a day for 48 weeks [3]. Though the rate of change in lung function were not different between arms, there was a significant reduction in the number of exacerbations in the 7% sodium chloride arm.
The recent laboratory data support the increased proposed efficacy of inhaled hypertonic sodium chloride over oral carbocisteine.

RCTs with follow up for a longer duration are needed now to improve the evidence base of both treatments and a head-to-head comparison between 7% sodium chloride and carbocisteine is required. In keeping with antimicrobial stewardship, it is key to promote evidence-based non-antibiotic therapies that help patients with COPD.

1.2 RATIONALE FOR STUDY

This study will provide knowledge on whether hypertonic sodium chloride is superior to carbocisteine in aiding sputum expectoration. In addition to improving sputum clearance, it is expected that there will be a prolongation in time to first exacerbation and overall a reduced number of exacerbations over one year.

It is expected that this study will be incorporated into future national and international COPD guidelines, which will facilitate the prescription of nebulised 7% sodium chloride in patients with COPD that have difficulty with sputum clearance.

The separate but linked process evaluation study will enhance implementation by identifying any barriers or facilitators to trial recruitment and implementation that can be addressed during the pilot phase. It will also add interpretation to results by contextualising outcomes within trial delivery and participant experiences; aid understanding of both clinician and participant adherence and fidelity to implementation processes that will not only benefit within trial participants but will also help for future implementation in the NHS if effectiveness is demonstrated.

It is hoped that this treatment will benefit future patients with COPD who struggle with sputum clearance. By improving health status and reducing exacerbations using an evidence-based therapy, this will have a personal benefit for patients, but will also reduce primary and secondary care resources by patients needing less access to these for management of exacerbations. From a societal perspective it is key to promote therapies that are non-antibiotic based. Our hypothesis is that nebulised 7% sodium chloride will aid sputum clearance and in addition has potential anti-bacterial and anti-viral properties that will both prolong the time to first exacerbation but will also reduce overall exacerbations. This approach has the potential to promote anti-microbial stewardship.

The treatment under investigation is a head to head comparison of nebulised 7% sodium chloride versus oral carbocisteine for 1 year. It is indicated for patients with COPD with chronic bronchitis and/or have associated bronchiectasis on computed tomography of the chest that have self-reported difficulty in expectoration.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

Assess whether nebulised 7% sodium chloride plus Active Cycle Breathing Technique (ACBT) is superior compared with carbocisteine plus ACBT when comparing the change in COPD Assessment Tests (CAT) over one year period.

2.1.2 Secondary Objectives

Over a one year period (+/- 21 days), to assess whether nebulised 7% sodium chloride plus Active Cycle Breathing Technique (ACBT) is superior compared with carbocisteine plus ACBT when comparing:

1. health related quality of life;
2. reducing exacerbations and prolonging the time to first exacerbation;
3. reducing identification of potential pathogen microorganisms from sputum samples and viruses from combined nose and throat swabs* (latter if taken as part of standard care);
4. reducing viral transmissibility;
5. stabilise or improve lung function;
6. health economic benefits.
7. adverse effects,
8. adherence

* It may not be possible to obtain viral nose and throat swab data from all participants, therefore sufficient data may not be collected to achieve this objective.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Assess whether nebulised 7% sodium chloride over one year (+/- 21 days) with ACBT airways clearance is superior compared with oral carbocisteine with ACBT over one year in leading to a 2 Unit or greater increase in the COPD Assessment Test (CAT).

2.2.2 Secondary Endpoints

The secondary endpoints will assess whether nebulised 7% sodium chloride with ACBT is superior compared with oral carbocisteine with ACBT in leading to:

1. Health related quality of life;

- An improved CAT score at 6 months compared with baseline;
- An improved quality of life assessment using the Leicester Cough Questionnaire and St. George's Respiratory Questionnaire at 6 months and 1 year. We will assess the mean change

from baseline to 6 months and baseline to one year between total LCQ and SGRQ scores between groups but also compare the number that have a 1.3 unit or more improvement in total LCQ scores and/or 4 unit or more improvement in SGRQ scores between groups ;

2. Reducing exacerbations and prolonging the time to first exacerbation;

- A reduced number of exacerbations over a one year period requiring antibiotic therapy and/or systemic steroid treatment;
- A prolonged time to first exacerbation requiring antibiotic therapy and/or systemic steroids over one year
- A reduced proportion of exacerbations needing antibiotic therapy over one year
- A reduced number of upper respiratory tract infections (URTI) over a one year period) assessed using the Wisconsin Upper Respiratory Symptom Survey-24 (WURSS-24)
- A reduced overall and COPD related hospital attendances/admissions over one year
- Frequency of use of nebulised 7% sodium chloride in exacerbations.

3. Reduction of potential pathogen microorganisms and viruses from sputum samples and combined nose and throat swabs;

- A reduced proportion being infected with a potential pathogenic organism and viruses at 6 months and one year (from sputum samples and combined nose and throat swabs (if taken as part of standard care))

4. Reduction in viral transmissibility (household contacts to participant and participant to household contacts)
5. Stabilise or improve lung function;
   Stable or improved Forced Expired Volume in 1 second (FEV1), forced vital capacity (FVC) and mid-expiratory flows at 6 months and one year
6. Health economic benefits;

- Cost per Quality Adjusted Life Year (QALY) a) over one year and b) modelled over a lifetime horizon

7. Compare adverse effects;

In addition, we will compare nebulised 7% sodium chloride and ACBT with oral carbocisteine and ACBT in:

- Adverse events over one year;

8. Adherence with interventions assessed by weekly participant charts and enquired at study appointments over one year.

3. STUDY DESIGN

Open pragmatic UK multi-centre parallel RCT with process evaluation and health economic analysis.

Participation is for one year to even out seasonal effects, in light of increased exacerbations over winter months. Participants will have a baseline appointment, midpoint appointment at 6 months (+/- 21 days)

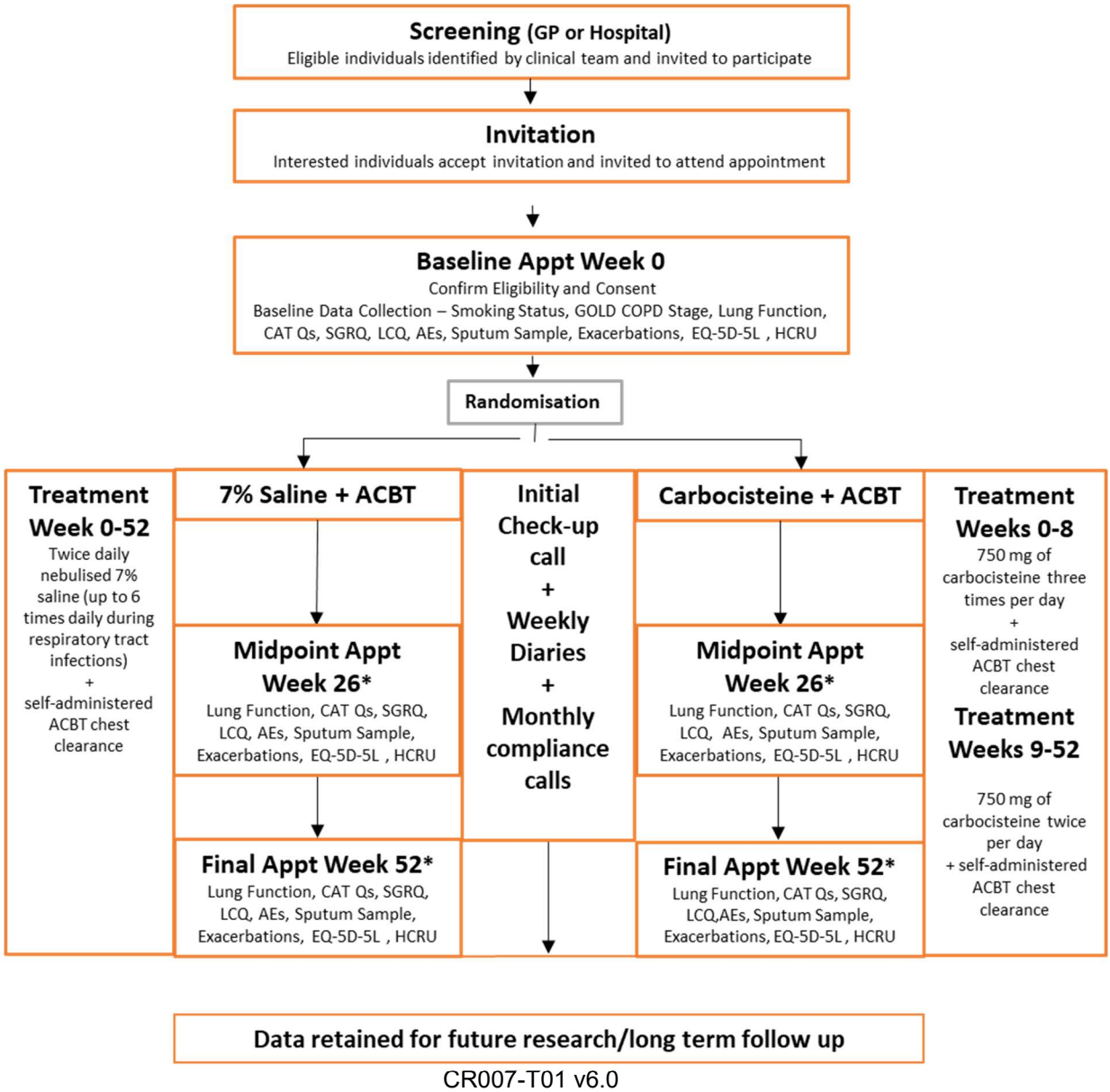
and final appointment at one year (+/- 21 days). Researchers will call the participants within 2 to 4 weeks of recruitment and every 8 weeks to review adherence to the intervention.

Participants will be randomised to receive either nebulised 7% sodium chloride plus ACBT or 750mg carbocisteine plus ACBT.

All participants will be taught chest clearance recommended as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD guidelines [31] and British Thoracic Society Bronchiectasis guidelines [32] using the ACBT technique by an online training video. This is then self-administered by the patient at home twice daily from 10-30 minutes maximum.

Trial appointments will take part at participating secondary care centres or remotely via telephone, videoconferencing and online methods.

The process evaluation will be led and sponsored by the University of Stirling and will be considered separate to the MucAct COPD trial. The relevant necessary research bodies will review the process evaluation study separately.



3.1 Pilot Study

The study has a built in pilot phase. By month 14 of the project, the following must have been achieved to allow progression to the full study:

Green (Go):

- Obtain approvals to start study recruitment, perform research nurse training, and commence recruitment at 4 or more sites;
- Randomise 50 or more patients;
- Adherence- 60% or more adherence by participants with intervention- defined as taking 60% or more of the investigational medicinal product (IMP) by analysis of the diary cards and phone calls every 8 weeks.

Amber (Take stock, and modify if necessary):

If green level is not achieved, but the following accomplished we will look to modify the project and continue:

- Obtain approvals to start study recruitment, perform research nurse training, and commence recruitment at 3 or more sites;
- Randomise 40 or more patients;
- Adherence- 50-59% adherence by participants with intervention- defined as taking 50-59% or more of the IMP by analysis of the diary cards and phone calls every 8 weeks.

Red (Stop):

The project will be stopped if any of the following is not achieved:

- Obtain approvals to start study recruitment, perform research nurse training, and commence recruitment at less than 3 sites;
- Randomise less than 40 patients;
- Adherence- less than 50% adherence by participants with intervention.

4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

860 participants with COPD that have either chronic bronchitis and/or associated bronchiectasis that have self-reported difficulty self-expectorating will be recruited from around 10-20 primary care and secondary care centres throughout the UK over a period of around 2.5 years.

4.2 INCLUSION CRITERIA

1. Patients ≥18 years old AND

2. Have COPD as the predominant respiratory diagnosis AND

3. Meet Medical Research Council (MRC) definition [13] of chronic bronchitis, defined epidemiologically as cough and sputum production for ≥3 months per year in at least 2 consecutive years and/or have associated bronchiectasis on computed tomography of the chest AND

4. Self-reported difficulty in expectoration (determined from the medical notes and/or participant). If from the participant, this will be documented in the medical notes.

4.3 EXCLUSION CRITERIA

1. Patients that do not have capacity to consent (determined by clinician or member of the research team).

2. Patients with an active malignancy.

3. Patients with a solid organ transplant.

4. Patients with active tuberculosis.

5. Patients who are in end-of-life care.

6. Patients who have had treatment with nebulised hypertonic sodium chloride, carbocisteine or any muco-active treatments within the past 30 days.*

7. Patients established on long-term antibiotic therapy for less than 3 months.

8. Patients who have had an exacerbation within the past 30 days requiring treatment with antibiotics and/or steroids

9. Known contraindication or intolerance to nebulised 7% sodium chloride or carbocisteine or any hypersensitivity to the active ingredients or the excipients of carbocisteine.

10. Active peptic ulceration; any known hereditary galactose intolerance, Lapp-Lactase deficiency or glucose galactose malabsorption; patients unable to swallow oral capsules.

11. Women who are pregnant or currently breastfeeding.

12. Women of childbearing potential** not taking appropriate contraception***. Contraception must be continued for a minimum of 30 days after the end of the IMP dosing schedule.

13. Participation in another Clinical Trial of an Investigational Medicinal Product (CTIMP) within the last 30 days.

14. Previous recruitment to the study.

15. Participants indicating that they are unable to comply with the study protocol prior to randomisation including those unable to complete participant questionnaires.

*If participants have been on treatment with nebulised 7% sodium chloride, carbocisteine or any muco-active treatments within the past 30 days, they need to come off these treatments for 30 days and remain clinically stable in order to be eligible for the study.

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

***Acceptable contraception in women of childbearing age is a “highly effective” contraceptive measure as defined by the Clinical Trials Facilitation Group and includes combined (oestrogen and progesterone containing) or progesterone-only contraception associated with inhibition of ovulation, or intrauterine device or bilateral tubal occlusion (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf).

4.4 CO-ENROLMENT

Co-enrolment will be allowed as outlined below and in accordance with the sponsor policy (POL008)

4.4.1 Observational Studies

Co-enrolment in observational studies will be permitted. For example, with studies that involve only the collection of data (e.g. questionnaires) or tissue samples (e.g. blood) will not require formal documentation or approval from the sponsor.

4.4.2 Interventional Phase CTIMP-CTIMP Co-enrolment

Enrolling a participant in the interventional phase of more than one CTIMP (i.e. a participant receiving IMP(s) from more than one trial concurrently) is not recommended and participants will be excluded from the study if they have participated in another CTIMP within 30 days.

4.4.3 Non-Interventional phase CTIMP-CTIMP Co-enrolment

In cases where participants are in long term follow-up (e.g. where follow-up data only is being collected) co-enrolment may be permitted. In such instances, the CTIMP-CTIMP Co-enrolment Checklist (POL008-F01) must be completed by the Sponsor Representative(s) in conjunction with the CI prior to the co-enrolment proceeding. Where necessary, the combined risk assessment may need to be appraised as per ACCORD SOP GS002 (Combined Risk Assessment).

4.4.4 CTIMP-NonCTIMP Co-enrolment

Participants who are active in the interventional phase of a non-CTIMP can be co-enrolled to a CTIMP provided the CTIMP-nonCTIMP Co-enrolment Checklist (POL008-F02) is be completed by the Sponsor Representative(s) in conjunction with the CI prior to the co-enrolment proceeding.
In addition, when considering permitting co-enrolment, investigators should be mindful of the potential burden upon participants, their families and research staff.

4.4.5 Accidental/Unintentional Co-Enrolment Identified Retrospectively

Investigators should aim to prevent accidental/unintentional co-enrolment by ensuring electronic and paper medical notes are checked for documentation of trial participation and by routinely asking participants if they are enrolled in another study prior to recruitment.
The Sponsor's representatives require that incidents of accidental/unintentional co-enrolment be reported to the Sponsor as a protocol deviation/violation so they can determine the appropriate course of action.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

At participating secondary care sites, potential participants may be approached during clinical visits to invite them to participate. Patients not due into clinic but who are identified as potentially suitable from database searches will be contacted by letter to notify them about the research or phoned and offered the opportunity to come in and discuss the study. In all cases, a member of the direct care team (which may include embedded research nurses) will make the first approach/contact. Potential participants will be provided with a participant information sheet and given the opportunity to ask the research team any questions relating to the study. Potential participants will be given as long as needed to decide whether to take part in the study and will be asked to contact the research team (by phone or by returning a consent to contact form) when they are happy to have a screening/baseline appointment. The research team will follow up with potential participants one week after the Patient Information Sheet (PIS) was provided where there has been no response.

Although most participants will be recruited at secondary care sites, some may be approached and recruited through primary care sites. At participating primary care sites, database searches will be completed by practice staff or GP network staff to identify potentially suitable participants. This process will be supported by the National Primary Care IT Solutions Working Group in England and the NRS Primary Care Network in Scotland.

Any participants not deemed suitable to be contacted about research would be removed from the search results. Potential participants will be contacted by letter to notify them about the study and they will be asked to contact the study research team at their local secondary care site if they are interested in taking part. They will be provided with a Consent to Contact form to return to the research team or they can contact them by phone.

5.2 CONSENTING PARTICIPANTS

The Principal Investigator (PI) (or member of the research team delegated by PI on the delegation log) will ensure that informed consent is obtained from each participant prior to entry into the study and completing any study specific procedures. The PI (or delegate) taking informed consent will be Good Clinical Practice (GCP) trained, suitably qualified and experienced. Due to the possible clinical need for some potential participants to take precautions such as shielding, the trial will also offer the options of remote consent. These will include telephone or videoconference consent with an appropriately trained and delegated member of the local research team or e-consent through secure, e-consent software.

5.2.1 Face-to-face Consent

When the potential participant has the appointment, they will be given the opportunity to ask the research team any questions they have.

When the participant confirms they are happy to participate, written informed consent will be obtained. A copy of the signed informed consent form will be given to the participant, original kept by the PI in the Investigator Site File at each research site and a copy filed in the participants medical notes. The participant's GP will be informed by letter of their participation in the study.

Capacity will be assessed, prior to consent, by the PI or a clinician responsible for the treatment of the participant. This assessment of capacity will be documented in the participant's medical records and in the CRF.

5.2.2 Telephone or Videoconference Consent

For participants unable to have a face-to-face visit consent can be obtained via telephone or video conference (using an approved system) with a member of the local research team. Ahead of the call, a recruitment pack will be sent to interested patients, this will include a copy of the PIS and two copies of the consent form (one for the patient to keep and one to be returned to site), and for women of child

bearing potential, a pregnancy test to be carried out at the time of the call. The result of this pregnancy test will be verified verbally and by showing the member of the research team via video conference. The member of the research team will discuss in full the trial with the potential participant and as with the face-to-face consent, opportunity will be given for questions to be asked and answers provided. If happy to participate, the participant will verbally confirm this with the member of the research team, and complete the consent paperwork provided. One copy of the consent form will be returned, to be counter signed by the member of the research team who conducted the interview, before further documentation is sent out to the patient, so that a copy can be filed in the participants medical notes and their inclusion documented, and the signed form retained in accordance with GCP by the local research team/PI. The participant's GP will be informed by letter of their participation in the trial.

5.2.3 Online Consent

For participants unable to have a face-to-face visit, and who are happy to consent electronically, this option will be made available to them. The same process as used for telephone or videoconference consent will be used and discussion with a member of the research team will be held after receiving a recruitment pack. However, rather than signing the paper consent, the participant will complete the consent form via an electronic signature software as an Advanced Electronic Signature (AES). Participation will be documented in their medical notes and a copy of the completed online form filed and a copy sent to the participant for their records. The participant's GP will be informed by letter of their participation in the trial.

5.3 SCREENING FOR ELIGIBILITY

Pre-screening for eligibility to participate will be completed by a member of the study team and this will be recorded on the screening log.

Participant eligibility will be verified by a clinical trial physician after informed consent has been obtained. Confirmation of eligibility will be recorded within the participants' medical records and in the Case Report Form (CRF).

The following assessments may need to be undertaken in order to confirm eligibility after consent but before a participant can be randomised:

- **A pregnancy test** for women of child bearing potential will be performed and the results recorded in the CRF. This is a study specific assessment. For those participants consented remotely (telephone or videoconference or online), a pregnancy test will be sent with their recruitment pack and done following completion of consent process (as detailed above) so the result can be viewed and confirmed by the member of the research team obtaining consent.
- **A GOLD score** (class 1-4) needs to be calculated prior to randomisation. A lung function assessment should be performed in order to calculate the GOLD stage. GOLD stages in

individuals with an FEV_1/FVC ratio under 0.7 are GOLD Stage 1 FEV_1 ≥80% percent predicted, GOLD Stage 2 50-79% percent, GOLD Stage 3 30-49%and GOLD Stage 4 <30% predicted. Lung function tests are undertaken as part of routine clinical care. For the purpose of the study, GOLD scores can also be calculated using Forced expired volume in 6 seconds- FEV_6 as the surrogate of FVC.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

All ineligible and non-recruited participants who are considered for entry into the study (defined as given written information about the study) will be recorded on the screening log and the reason given for being ineligible and/or not recruited e.g. patient decision, clinician decision, inclusion and/or exclusion criteria prohibited entry.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

After assessment for eligibility and consent, a member of the research team will perform the randomisation using a web-based randomisation service managed by the Edinburgh Clinical Trials Unit (ECTU). Participants will be randomised on a 1:1 basis to nebulised 7% sodium chloride plus ACBT or 750mg carbocisteine plus ACBT.
The randomisation system will include allocation concealment and stratification for current smoking status, COPD severity (GOLD class 1 and 2 versus 3 and 4). Further details will be put into a separate randomisation specification.

5.5.2 Treatment Allocation

Following randomisation, both the participant and the Investigator will be notified of the assigned treatment allocation. A study prescription will be generated every 3 months - at the baseline, at 3 months, at 6 month (+/- 21 days) appointments and at 9 months and the treatment will be dispensed by the pharmacy at the local trial site. To allow for participants increasing the dose of 7% sodium chloride from 2 times a day to a minimum of 4 times a day and up to 6 times a day during respiratory tract infections, participants will be given spare packs to ensure sufficient supply. The research team will provide dosing instructions.

Ideally, participants will collect their allocated treatment from the pharmacy in person. However, as detailed above, for clinical reasons they may be unable to do so, therefore a representative can collect the IMP on their behalf. If there is no available representative the local research team will use an approved same day courier (adhering to local SOPs) to deliver the IMP or intervention supplies to the participant's home. The local team will confirm that the participant will be available to receive delivery before booking; this will ensure that the IMP is delivered directly to the participant. The courier will provide the local research team with documentation confirming delivery to the participant.

5.5.3 Emergency Unblinding Procedures

The study is not blinded so there is no procedure in place.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case record form, if possible. The participant will have the option of withdrawal from:

(i) study medication with continued study procedures and collection of clinical and safety data;

(ii) all aspects of the trial but continued use of data collected up to that point. To safeguard rights, the minimum personally-identifiable information possible will be collected.

6. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification

Any brand/generic of 7% nebulised sodium chloride stocked in NHS pharmacy is acceptable. Examples of trade names are; Resp-Ease 7%, NebuSal. This list may not be exhaustive and examples are representative. These are commonly used medications and the study team do not anticipate any supply issues. Site hospital pharmacies will be responsible for the unscheduled resupply of 7% nebulised sodium chloride and each site hospital responsible for the supply of nebulisers. Each site pharmacy should make arrangements to supply stock according to local circumstances. Site pharmacists should maintain communication with site investigators regarding available stock, to ensure that participants are only enrolled when sufficient stock is available. Sites may ring–fence stock if that is the optimal method of ensuring sufficient stock is available for the trial. Accountability will be documented in accordance with local policy/practice.

6.1.2 Study Drug Manufacturer

Not applicable. Any preparation of 7% nebulised sodium chloride which is certified for use as part of a CE marked medical device and is stocked by local hospital pharmacies at the participating sites, may be employed in this study. The CE marked medical device used will be decided by the site.
A representative of the IMP, Resp-Ease 7%, is manufactured by Venture Healthcare Ltd.

6.1.3 Marketing Authorisation Holder

Resp-Ease 7% is certified in accordance with EU Directive 93/42/EEC, as amended.

Laboratoire Unither SAS

Espace Industriel Nord

151 rue André Durouchez

CS 28028

80084 Amiens Cedex 2

6.1.4 Labelling and Packaging

No specific arrangements are planned for labelling since we will use the licensed medicinal products that are currently available in the UK and will be used according to their marketing authorisation. The IMPs will not require a study specific label as they will be labelled as standard.

6.1.5 Storage

Storage and dispensing of the IMP will be undertaken by the local hospital pharmacy department at each participating site. The IMP will be kept in a secure place at each hospital pharmacy under conditions specified in the local internal procedures, but should not be stored above 25°C and should not be refrigerated or frozen.

6.1.6 Regulatory Release to Site

Not applicable.

6.1.7 Destruction of Study Drug

Any unused medication at the end of each prescription period (3months) should be discarded in accordance with local policy/practice. If the participant is attending study visits in person, any unused medication can be brought with them to be discarded by the research team in accordance with local policy/practice. If required, participants can also return their unused medication to their community pharmacy for destruction.

6.1.8 Summary of Product Characteristics (SPC) Booklet or Investigators Brochure

The Resp-Ease 7% Summary of Product Characteristics (SPC) is provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Sponsor) and is filed in the TMF.

6.2 COMPARATOR STUDY DRUG

6.2.1 Study Drug Identification

Carbocisteine 375mg Capsules. This is a commonly used medication and the study team do not anticipate any supply issues. Each site pharmacy should make arrangements to supply stock according to local circumstances. Site pharmacists should maintain communication with site investigators regarding available stock, to ensure that participants are only enrolled when sufficient stock is available. Sites may ring–fence stock if that is the optimal method of ensuring sufficient stock is available for the trial. Accountability will be documented in accordance with local policy/practice.

6.2.2 Study Drug Manufacturer

Not applicable. Any preparation of Carbocisteine which has marketing authorisation in the UK and is stocked by local hospital pharmacies at the participating sites, may be dispensed in this study.
A representative manufacturer of Carbocisteine is Accord Healthcare Ltd.

6.2.3 Marketing Authorisation Holder

An example of a Carbocisteine MA Holder is Accord Healthcare Limited and the MA number is PL 20075/0670.
Accord Healthcare Limited
Sage House
319 Pinner Road
North Harrow
Middlesex
HA1 4HF
United Kingdom

6.2.4 Labelling and Packaging

No specific arrangements are planned for labelling since we will use the licensed medicinal products that are currently available in the UK and will be used according to their marketing authorisation. The IMPs will not require a study specific label as they will be labelled as standard.

6.2.5 Storage

Storage and dispensing of the IMP will be undertaken by the local hospital pharmacy department at each participating site. The IMP will be kept in a secure place at each hospital pharmacy under conditions specified in the local internal procedures but should be stored below 25ºC.

6.2.6 Regulatory Release to Site

Not applicable.

6.2.7 Destruction of Study Drug

Any unused medication at the end of each prescription period (3months) should be discarded in accordance with local policy/practice. If the participant is attending study visits in person, any unused medication can be brought with them to be discarded by the research team in accordance with local policy/practice. If required, participants can also return their unused medication to their community pharmacy for destruction.

6.2.8 Summary of Product Characteristics (SPC) Booklet or Investigators Brochure

The NHS does not have a preferred brand or generic carbocisteine.

Each hospital pharmacy may stock several brands and these may change over the course of the study. The pharmacy can dispense any brand of carbocisteine currently in stock. A representative Summary of Product Characteristics (SmPC) is provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Sponsor) and is filed in the TMF.

6.3 DOSING REGIME

6.3.1 Nebulised 7% Sodium chloride Arm

The active arm will receive twice daily nebulised 7% sodium chloride + self-administered ACBT chest clearance. The participants are self-administering nebulised 7% sodium chloride and will be allowed to increase the frequency of use up to a maximum of 6 times per day during respiratory tract infections (minimum four times daily where possible).

Participants allocated to the nebulised 7% sodium chloride arm will be instructed to administer a 1 x 4 mL ampoule twice daily for 52 weeks using the nebuliser provided by their local study team. Nebulisation takes less than 10 minutes. Participants will be given training on cleaning and usage of the nebuliser during their baseline appointment and provided with an information sheet. This training will be completed either via videoconferencing or in person.

Some patients have bronchospasm with nebulised 7% sodium chloride. If these symptoms develop, treatment with nebulised 2.5mg salbutamol is recommended prior to taking the nebulised 7% sodium chloride. Nebulised 2.5mg salbutamol can also be used post hypertonic sodium chloride if needed. This can be prescribed as part of the participant's clinical care if required.

Most patients manage with this adjunct treatment. Again, in the event of clinical concern, the treatment would be stopped. The study medication will be prescribed every 3 months - at the baseline appointment, at 3months, at the 6 month (+/- 21 days) appointment and at 9 months

6.3.2 Carbocisteine Arm

The comparator arm with carbocisteine will receive oral carbocisteine (750 mg of carbocisteine three times per day for 8 weeks, reducing to 750 mg twice per day over 44 weeks) + self-administered

ACBT chest clearance. The dose of carbocisteine is in accordance with the British National Formula (BNF). The study medication will be prescribed every 3 months - at the baseline, at 3 months, at the 6 month (+/- 21 days) appointment and at 9months

6.4 DOSE CHANGES

If there is gastro-intestinal intolerance with the carbocisteine, a dose reduction can be tried (375mg three times per day for 8 weeks if in the initiation phase and 375mg twice daily in the maintenance phase). If a dose reduction occurs, this will be documented in the CRF and the participant's medical notes.

There will be no change of the HS dose (7%).

6.5 PARTICIPANT ADHERENCE

The following will be completed to assess adherence and fidelity: review the weekly participant diaries; study team will perform calls every 8 weeks to all participants; ask all participants about adherence at each study appointment.

Non-adherence is defined as a participant taking less than 50% of their allocated IMP. The average adherence across the study should be 50% or greater in order for the study to continue beyond the pilot phase.

Non-adherence to allocated treatment will be recorded in the CRF and does not need to be recorded/reported as a deviation or violation. Compliance will be tabled, reported to and monitored by the TSC and DMC. Review of compliance will be added to meeting agendas to ensure action is taken when appropriate.

The process evaluation will also explore issues of adherence within interviews and provide feedback to the study team about issues that can be addressed during the study without impinging on fidelity to the intervention.

The phone calls every 8 weeks will be standardised and we will record at least one phone call from each research site for the process evaluation. This will be reviewed for adherence and any feedback provided to the sites but will not form part of the analysis.

6.6 OVERDOSE

Substantial oral ingestion of 7% sodium chloride may require the use of a diuretic to remove excess sodium.

To minimise the risk of overdose, participants will be given training on cleaning and usage of the nebuliser for oral ingestion of 7% sodium chloride during their baseline appointment and provided with an information sheet. This training will be completed either via videoconferencing or in person.

For carbocisteine overdose, gastric lavage may be beneficial, followed by observation. Gastrointestinal disturbance is the most likely symptom of carbocisteine overdose.

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

Salbutamol 2.5mg ampoules via the nebuliser can be used if there is bronchospasm with nebulised sodium chloride both before and after the nebulised sodium chloride if required. Any preparation of Salbutamol 2.5mg which has marketing authorisation in the UK and is stocked by local hospital pharmacies at the participating sites, may be dispensed in this study. Use of Salbutamol 2.5mg is not expected in all patients however, if it is required, the participant's local hospital will supply the initial prescription which will then be continued by their GP.

6.7.2 Permitted Medications

For those that have met the inclusion and exclusion criteria, the participants are able to take all their prescribed medications. If a new long term medication is prescribed (more than 28 days), the participant will be advised to contact the study team, to ensure there are no contraindications.

6.7.3 Prohibited Medications

Patients who have had treatment with nebulised 7% sodium chloride, carbocisteine or any muco-active treatments within the past 30 days are excluded from the study. If they withdraw from these treatments and remain clinically stable they would be eligible for the study after a 30 day period.

If participants take the study drug which they have not been allocated during the study, then this will be documented in the CRF. Intention to treat analysis will be used.

There are no known interactions between carbocisteine and other medicinal products or other forms of interaction so there are no prohibited medications associated with it.

There are no known interactions between 7% sodium chloride and other medicinal products or other forms of interaction so there are no prohibited medications associated with it.

7. STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

There are no specific safety assessments required for the study or comparator drug. Pregnancy testing will be carried out as part of eligibility assessment as pregnant women should be excluded from the trial.

7.2 STUDY ASSESSMENTS

	Screening Pre-Rando Week 0	Baseline Post-Rando Week 0	Weekly Diary Card	Exacer-bation Diary	Check-up Call$	8-weekly Call#	3 months	Midpoint Appt (6months)^	9 months	Final Appt (1 year)^
Eligibility	X									
Pregnancy test (for women of child bearing potential)	X									
Consent	X									
Smoking status	X									
GOLD COPD Stage	X									
Lung function assessment*	X							X		X
Record of vaccinations (influenza, pneumococcal and COVID)	X							X		X
Randomisation		X								
CAT Questionnaire		X						X		X
St. George's Questionnaire		X						X		X
Leicester Cough Questionnaire		X						X		X
ACBT Training		X								
Nebuliser Training (Intervention arm only)		X								
IMP Prescription		X					X	X	X	
IMP adherence			X			X		X		X
Household contact viral transmissibility data			X			X				
Viral test history #		X				X		X		X
Record of Exacerbations			X	X		X		X		X
WURSS-24 Survey				X		X				
Adverse Events		X	X		X	X		X		X
Sputum Sample (if spontaneous)		X						X		X
EQ-5D-5L		X		X		X		X		X
Health Care Resource Use (HCRU)		X						X		X

*Post bronchodilator (only if on long acting bronchodilator therapy) Forced expired volume in 1 second, Forced vital capacity (Forced expired volume in 6 seconds- FEV6 will be used as the surrogate of FVC) and mid- expiratory flows (FEF 25-75).

This avoid participants having to withhold their bronchodilator therapy and allows consistent comparisons.
$ The research team will phone participants 2-4 weeks following their baseline visit to enquire about adverse events and how the participant is getting on with their allocated treatment.
^ Appointments are permitted to be +/- 21 days of the timepoint**.** # Appointments are permitted to be +/- 7 days of the timepoint.
# If participants have had any viral testing performed as part of standard care during their participation in the trial, this data will be collected on the eCRF

For safety reasons, during the COVID 19 pandemic, the study team would recommend;

- Performing airway clearance techniques by yourself in a room with an open window.
- If using the nebuliser, perform by yourself in a room with an open window.
- Other family members not to enter the room for 60 minutes after you have finished.
- Others helping and handling the mask and nebuliser equipment (if using this) should be advised on good hand hygiene to minimise risk of infection spread.

If a patient is attending a visit remotely, the research team will post all relevant questionnaires, information and sample collection kits for the patient to do at home.

7.3 ADHERENCE ASSESSMENTS

Adherence will be reviewed in two ways - the Weekly Diary Cards and through phone calls every 8 weeks to the participants and recording adherence each study appointment as outlined in section 6.5.

Adherence will also explored by the process evaluation team.

7.4 LONG TERM FOLLOW-UP ASSESSMENTS

Participation in the study is for 1 year with the final appointment being completed at 52 weeks +/- 21days.

Personal data will be stored for a maximum of 10 years to conduct future ethically approved studies. The availability of personal data, including NHS number (e.g. CHI number), will allow us to perform record linkage with other national health registries to ascertain how the intervention affects the participants' future health status. We will seek consent from participants to retain their data for future research and this will be optional on the consent form. Any future research would be approved by a research ethics committee first. Long-term data linkage and data sharing can be facilitated by the BREATHE Health Data Research Hub and will not involve the transfer of any personal data.

Personal data will only be as held as long as it is necessary and then the data will be destroyed.

7.5 STORAGE AND ANALYSIS OF SAMPLES

A sputum sample will be collected in a sputum pot as part of routine clinical care at the baseline, midpoint and final appointments if the participant can spontaneously produce one. It will not be

recorded as a deviation if a sample cannot be collected. These will undergo routine microbial testing for pathogenic organisms and the results recorded on the CRF. These may be retained at some participating centres where appropriate storage facilities permit and/or transferred to Edinburgh to the Centre for Inflammation Research, Queen's Medical Research Institute for long term storage for the purpose of future research. Consent will be obtained from all participants for this.

If a participant is being seen remotely, a sputum pot will be posted to the participant. If producing sputum, the study team will request the sample be handed in to their local GP practice or their local hospital for processing as soon as possible after the participant collects the sample (preferably within 24 hours). The study team will ask the sputum sample to be stored in the fridge until delivery. All sputum samples will be analysed in the NHS microbiology labs of the respective trial site, in accordance with standard of care.

8. DATA COLLECTION

The following data will be collected by a trained and delegated member of the study team (apart from where it is self-reported by the participant). All appointments will be either face to face or remotely via telephone, videoconferencing and online methods.

8.1 Pre-Screening

A member of the study team will complete pre-screening using the patient's medical records. If the patient is potentially eligible, their name and date of birth will be collected for the purposes of making an appointment. Identifiable data will not be recorded on the eCRF until after consent has been obtained.

Patients who do not want to participate in the main study will be asked to complete a 'Consent to Contact' form if they are willing to take part in the process evaluation interview study only. The contact information they provide on the form will be added to the eCRF so the process evaluation team can access it.

8.2 Screening and Baseline Appointment

When the participant attends the study appointment, the study team will consent the participant, complete screening and if eligible will randomise them. If ineligible, or unwilling to participate, this will be documented in the screening log. The eligibility form and pre-randomisation information (including smoking status and GOLD COPD stage) will be completed on the eCRF. A lung function assessment will need to be performed at the screening/baseline appointment to confirm eligibility. The results from this lung function assessment will also be used as baseline data. This will be performed using the spirometer provided for the study so that consistent readings are obtained and completed according to British Thoracic Society Guidelines. Lung function assessment is measured by post-bronchodilator

spirometry (only if on long acting bronchodilator therapy) (Forced expired volume in 1 second, Forced vital capacity (Forced expired volume in 6 seconds- FEV6 will be used as the surrogate of FVC) and mid- expiratory flows (FEF 25-75)). Participants will be asked to take their regular inhalers at least 60minutes before the assessment. Participants will also be reminded to avoid eating a large meal for 2 hours before the test, avoid caffeine on the day of test, and to avoid vigorous exercise for 30 minutes before the test. For virtual appointments, the spirometry will be supervised by the research nurse. To avoid any error in the communication of this result, participants will be asked to show the member of the research team the spirometry results through video link, communicate them verbally and document them in their participant diaries.

The study team will complete the post-randomisation baseline CRF to collect:

The participant will be asked to complete a questionnaire recording:

Leicester Cough Questionnaire measures quality of life and assesses chronic cough.

St. George's Respiratory Questionnaire to measure health status (quality of life).

COPD Assessment Test to measure the impact of COPD on wellbeing and daily life.

EQ-5D-5L to measure quality of life

Health Care Resource Use.

Questionnaires will be completed online unless the participant is unable or unwilling to access them this way. If a paper version of the questionnaire is used, the study team will review the questionnaire for completeness and enter this into the CRF.

The study team will collect any Adverse Events as per section 12.2 of the protocol.

Collection of sputum sample and entry of results sample analysis into eCRF (if applicable).

Collection and entry of results from any viral swab tests taken as part of standard care

Participants will be given information about where to access the ACBT technique video training. ACBT training will be documented in the participant's medical records.

Participants in the intervention arm will be provided with training on how to use and clean their nebuliser. Training on how to use and clean the nebulisers will be documented in the participant's medical records.

Participants will be given their prescription and asked to collect their allocated medication from pharmacy. Ideally, participants will collect their allocated treatment from the pharmacy in person.

However, as detailed above, for clinical reasons they may be unable to do so, therefore a representative can collect the IMP on their behalf. If there is no available representative the local research team will use an approved same day courier to deliver the IMP and if relevant, accompanying study specific equipment (e.g. nebuliser) to the participant's home. The local team will confirm that the participant will be available to receive delivery before booking; this will ensure that the IMP is delivered directly to the participant. The courier will provide the local research team with documentation confirming delivery to the participant.

A letter will be sent by the study team to inform the GP that their patient is taking part in the study.

8.3 Weekly Diary Cards

The Weekly Diary Card will be provided to the trial participants to be completed in paper form. . If the Weekly Diary Card is not completed, a reminder will be sent by text message/email or phone call. Participants will be asked to return these to the research team by post for entry into the eCRF and review ahead of the 8 weekly telephone call. The Weekly Diary Cards will record IMP adherence, record of exacerbations, new medications and potential Adverse Events. Participants will also be asked specifically about their COVID-19 status.

A record of exacerbations: Participants will be asked about exacerbations in the Weekly Diary Card. They will be asked to record details of the exacerbation in the Exacerbation Diary, including what treatments were received. They will be asked to complete the Wisconsin Upper Respiratory Symptom Survey-24 and EQ-5D-5L, on a daily basis, until the exacerbation has stopped up to a maximum for 14 days. All exacerbations will be treated as per standard care for that participant. Some participants will use a self-management plan to self-treat exacerbations at home and some will prefer to see their GP.

8.4 Exacerbation Diary

If an exacerbation is reported in the Weekly Diary card, the participant will be asked to complete the Exacerbation Diary, using the same methods described in section 8.3, until the exacerbation has stopped up to a maximum for 14 days. This will record details of their exacerbations, new medications, Wisconsin Upper Respiratory Symptom Survey and EQ-5D-5L.

8.5 Telephone Calls (every 8 weeks)

The research team will contact the participant every 8 weeks by telephone (+/- 7 days or as soon as possible after receipt of diary) to review the information provided in the Weekly Diaries and Exacerbation Diaries about adherence to the study medication, exacerbations, Wisconsin Upper Respiratory Symptom Survey, EQ-5D-5L and any AEs/SAEs.

8.6 Midpoint Appointment

The study team will complete the Midpoint CRF to collect:

Lung function assessment

IMP accountability

A record of exacerbations

Adverse Events

Results of sputum sample and viral swab analysis (if applicable)

The participant will be asked to complete questionnaires the day before the appointment recording:

Leicester Cough Questionnaire

St. George's Respiratory Questionnaire

COPD Assessment Test

EQ-5D-5L

Health Care Resource Use

If paper questionnaires are used, the study team will review the questionnaires for completeness and enter them into the eCRF.

Participants will be given their prescription and asked to collect their allocated medication from the pharmacy. Ideally, participants will collect their allocated treatment from the pharmacy in person. However, as detailed above, for clinical reasons they may be unable to do so, therefore a representative can collect the IMP on their behalf. If there is no available representative the local research team will use an approved same day courier to deliver the IMP to the participant's home. The local team will confirm that the participant will be available to receive delivery before booking; this will ensure that the IMP is delivered directly to the participant. The courier will provide the local research team with documentation confirming delivery to the participant.

8.7 Final Appointment

The study team will complete the Final Appointment CRF to collect:

Lung function assessment

IMP accountability

Adverse Events

Results of sputum sample and viral swab analysis (if applicable)

A record of exacerbations

The participant will be asked to complete questionnaires the day before the appointment recording:

Leicester Cough Questionnaire

St. George's Respiratory Questionnaire

COPD Assessment Test

EQ-5D-5L

Health Care Resource Use

If paper questionnaires are used, the study team will review the questionnaires for completeness and enter them into the eCRF.

8.8 SOURCE DATA DOCUMENTATION

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records where source data are recorded for the first time.
The location of the source data is detailed in the MucAct COPD Source Data Plan.

8.9 CASE REPORT FORMS

Data will be directly entered into the eCRF but where not possible then this will be collected via source data collection sheets and transcribed in a timely manner.

All case report forms must be reviewed and approved by the ACCORD Monitor prior to use (see ACCORD SOP CR013 CRF Design and Implementation) and all electronic case report forms are subject to Sponsor approval.

8.10 STUDY DATABASE

The study database will be created and maintained by ECTU. Trained and delegated members of the study team will be given password-protected logins to the database to complete data entry. The data will be stored in a secure server in the University of Edinburgh for the minimum retention period for the study data.

9. DATA MANAGEMENT

9.1.1 Personal Data

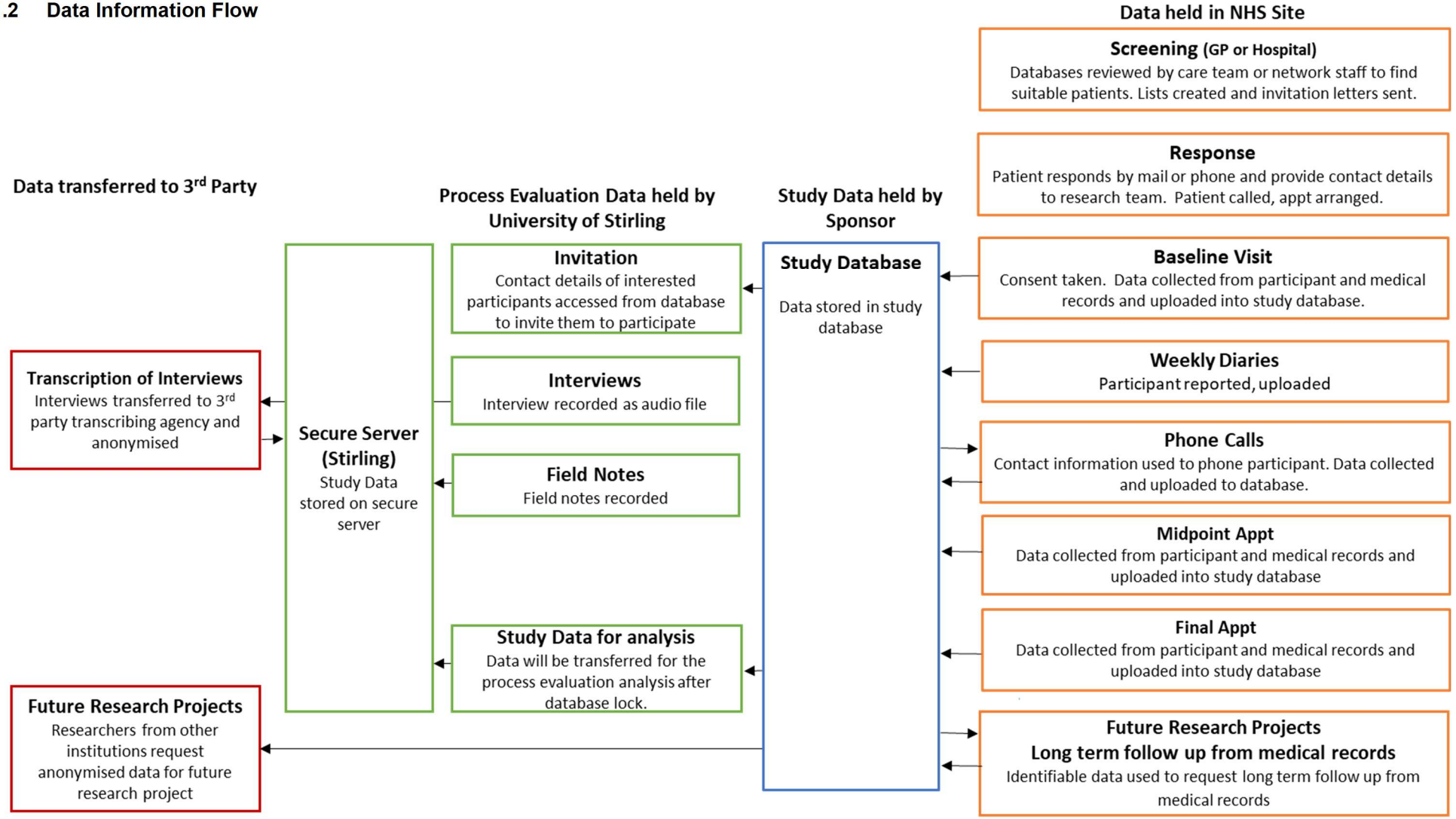
The following personal data will be collected as part of the study;
Name
Address
Telephone Number
Email Address
Date of birth
NHS number (e.g. CHI number)
Demographics
Medical history

Personal data will be stored indefinitely to conduct future ethically approved studies. The availability of personal data will allow us to perform record linkage with other national health registries to ascertain how the intervention affects the participants' future health status.

Personal data will be stored by the study team on NHS computers (desktop and laptop). Computers will be password protected and kept in locked offices. All paper files containing personal data will be held in filing cabinets in NHS offices that will be locked when unattended. Access to the study documents will be by the study team only.

Edinburgh Clinical Trials Unit will provide and maintain a secure web based database compliant with the relevant regulations and Sponsor SOPs. Data will be entered by those staff delegated to do so on the delegation log held at site.

9.1.2 Data Information Flow



9.1.3 Transfer of Data

Identifiable personal data collected or generated by the study from a proportion of participants will be transferred to the University of Stirling for the purposes of carrying out the process evaluation study. There will be an agreement for the sharing of data between the two studies.

9.1.4 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

9.1.5 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

10. STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

We estimate there will be 2000-4000 patients per centre with COPD, of whom ~20% (n=400-800) will meet eligibility criteria, and that 10% of these will agree to be randomised (n=40-80).

There are differing opinions on the Minimal Clinical Important Difference (MCID) in the CAT questionnaire in the literature ranging between 1·6 and 2·0 [10,11]. In a 2-arm trial, with 90% power, 5% level of significance, to find a MCID of 1.6 in the CAT questionnaire we would need 427 per group; and to find a MCID of 2.0 we would need 274 participants. These calculations use a standard deviation of 9.0 [14,15], which can be reduced to 7.2 [16] assuming that the within person correlation in baseline/follow-up CAT score is 0.6 [10]. We think that nebulised sodium chloride may be less well tolerated than other treatments, leading to participants ceasing treatment or crossing to the other treatment arm (we will follow participants up regardless of treatment adherence), and diluting the observed treatment effect. We therefore plan to recruit 430 per group which will allow for the lower of the suggested MCIDs if there is good adherence and no missing data and will allow for dilution of the treatment effect at the larger MCID if there is poorer adherence and some missing data. For instance, if 15% of the nebulised sodium chloride group cross to carbocisteine, then a treatment difference of 2.0 would reduce to 1.7, and the required sample size would be 378. If there is 12% missing data, then 378 becomes 424. We realise that in this latter situation, under intention-to-treat, the measured treatment effect would be 1.7 rather than 2.0 but this MCID is still plausible as it is within the range of 1.6 to 2.0. Therefore, the total trial size is 860 participants.

If participants are willing, we will follow them up regardless of their level of adherence to their allocated trial medication. The primary analysis will be intention to treat. The sample size takes non-adherence into account.

10.2 PROPOSED ANALYSES

The primary analysis of the primary outcome will be based on an intention-to treat population and will use linear regression (with appropriate transformations to achieve Normality) to compare the 12-month CAT scores between allocated treatment groups, adjusting for baseline CAT score and stratification variables. Statistical significance will be at $p \leq 0.05$, and tests will be 2-sided tests for a difference. The adjusted difference in the mean CAT scores between treatment groups, plus its 95% confidence interval will be presented. If the level of missing data is high enough that the method of accounting for it might influence the results, then we will use multiple imputation, assuming data are missing at random. Similar methods will be used for continuous secondary outcome measures. Time to event will be analysed using Cox proportional hazards, if the assumptions of proportionality hold. All statistical analyses will be fully specified in a comprehensive Statistical Analysis Plan, authored by statisticians blind to accruing unblinded resultsand signed off prior to database lock. The choice of methods in this plan will consider the accruing blinded data (e.g. whether scales are Normally distributed, whether missingness requires accounting for in analysis). Processes will follow relevant ECTU and ACCORD Standard Operating Procedures and Working Practice Documents for Clinical Trials of an Investigational Medicinal Product, including involving sufficient statisticians in the study to allow for appropriate blinding where needed.

11. HEALTH ECONOMICS AND DATA ANALYSIS

To maximise UK policy relevance, health economic analysis will follow National Institute for Health and Care Excellence (NICE) reference case recommendations [17] including: Adoption of an NHS and PSS (personal social service) costing perspective for primary analyses; cost-utility approach (results presented in terms of incremental cost per QALY derived from EQ-5D-5L); discount rate of 3.5% for both costs and QALYs (where applicable); use of probabilistic sensitivity analysis (PSA); and provision of value of information analysis (VoI) where appropriate to inform future research [17].

Two forms of analyses will be undertaken: A within trial analysis of the 12 months observed period, and longer-term economic modelling which extrapolates these results over a lifetime horizon in order to account for mortality.

NHS resource use will (including GP/Practice & District nurse consultations, community prescribing, physiotherapy, other outpatient visits, NHS Direct/NHS24/111 calls, ambulance trips, A&E admissions, and inpatient admissions), will be combined with standard UK price weights [33] [34] published at the time to generate costs. The latest financial year for which at least one study participant provides data, and prices are available will be selected as base year.

The NICE recommended algorithm at time of analysis will be used to generate health utility scores from EQ-5D-5L data. In order to capture the short dips in health utility expected during an exacerbation, which may be missed using a standard area under the curve approach, each patient's QALYs will be based on the number of days with and without exacerbations using EQ-5D-5L average scores observed through the study participants diaries.

Full details of these analyses will be specified in a comprehensive Health Economic Analysis Plan, authored by the study health economist(s), and signed off by the PI prior to analysis.

12. PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SPC) Booklet.

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after informed consent until the final 12 month follow up appointment must be recorded in the CRF or AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

12.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC) booklet or Investigators Brochure.

12.2 IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs/SAEs at every appointment during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded. Where a participant experiences an event that relates to a pre-existing medical condition or expected worsening of an underlying condition, this will be recorded in the patient's medical notes and not reported as an AE.

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

12.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the study team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

12.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study. Exacerbations relating to a patient's COPD will be recorded as part of study outcomes.

12.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study and, if meeting seriousness criteria, reported to the Sponsor as SAEs. Events that are consistent with the expected progression of the

underlying disease should not be recorded as AEs. Examples of underlying conditions where deterioration is expected in this population are asthma, COPD and bronchiectasis.

12.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the study team who has been delegated this role.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

12.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

12.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.

- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

12.4.3 Assessment of Expectedness

If the event is an AR the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SPC Booklet.

The event may be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the SPC Booklet.

Unexpected: the AR is not consistent with the toxicity in the SPC Booklet.

Fatal and life threatening SARs should usually be considered unexpected. Fatal SARs can only be expected for IMPs with an MA in the EU, when it is clearly stated in the list of ARs of the SPC (Section 4.8) that the IMP causes fatal SARs.

12.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the CRF/AE log or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

12.5 RECORDING OF AEs

All adverse events for each participant will be recorded on the AE log and will be assigned the appropriate MedDRA Systems Organ Class (SOC) code.

Signs and symptoms of pulmonary exacerbations collected as outcomes of the study will not be recorded as AEs. Expected deteriorations of a medical condition will also not be recorded as AEs.

12.6 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance **within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

Signs and symptoms of pulmonary exacerbations collected as outcomes of the study will not be reported as AEs. Therefore, if a patient requires hospitalisation or prolongation of existing hospitalisation as a result of an exacerbation this will not be reported as an SAE.

12.7 REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for pharmacovigilance reporting on behalf of the co-sponsors (The University of Edinburgh and NHS Lothian).

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the study). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

12.8 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

12.9 PREGNANCY

Although pregnancy is not considered an AE or SAE; as a matter of safety, the Investigator will be required to record any female participant's pregnancy or any pregnancy of a female partner of a male participant, who became pregnant while participating in the study. The Investigator will need to record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

All pregnant female participants and pregnant partners of male participants will be followed up until the outcome of the pregnancy.

13. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 TRIAL MANAGEMENT GROUP

The study will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager and Coordinating Nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the study team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

13.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the study. The terms of reference of the Trial Steering Committee and the names and contact details will be detailed in the TSC Charter.

13.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the study. The terms of reference of the Data Monitoring Committee, the outline of the DMC report, and the names and contact details will be detailed in the DMC Charter. The DMC Charter will be signed by the appropriate individuals prior to the study commencing.

13.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit study related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

13.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input

will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to study design.

13.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary.

14. GOOD CLINICAL PRACTICE

14.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP) [35].

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

14.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

14.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

14.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the study team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

14.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

14.3.3 Data Recording

The Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

14.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the

required documentation is available in local Investigator Site files ISFs. Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

14.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

14.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Identifiable clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any identifiable data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential identifiable information to other parties.

14.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the General Data Protection Regulation with regard to the collection, storage, processing and disclosure of personal information. Access to identifiable personal information will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any identifiable personal data, and will be written so as to minimize the risk of identifying individual participants.

15. STUDY CONDUCT RESPONSIBILITIES

15.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Sponsor for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

15.2 PROTOCOL NON COMPLIANCE

15.2.1 Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

15.2.2 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

15.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every quarter. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.Deviation logs / violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email.. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

15.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA (clintrialhelpline@mhra.gsi.gov.uk), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

15.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

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

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

15.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

The anonymised study dataset will be retained for future research as detailed in section 17.3.

15.6 END OF STUDY

The end of study is defined as 6 months from the last participant's last appointment. Database-lock and site close-out visits will occur as soon after the respective last participant's appointment as practical.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study.

Upon completion of the study, the Investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

The Investigator will submit a short confirmatory e-mail to the MHRA (CT.Submission@mhra.gsi.gov.uk) once the result-related information has been uploaded to EudraCT, with 'End of trial: result-related information: EudraCT XXXX-XXXXXX-XX' as the subject line. The Sponsor(s) will be copied in this e-mail (QA@accord.scot). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

15.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

If participants wish to continue the study drug after the end of the study, they should discuss this with their GP.

15.8 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

16. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

16.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analyzed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

16.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to

publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

The findings will be presented at local, national and international meetings. The PPI group and the British Lung Foundation will help disseminate the results to professionals and affected members of the public and the paper will be submitted for publication in an influential and widely read medical journal with high impact factor.

16.3 DATA SHARING

All data requests should be submitted to the Chief Investigator for consideration. Access to anonymised data may be granted following review by CI and Edinburgh Clinical Trials Unit.

16.4 PEER REVIEW

The study was peer reviewed during the NIHR HTA application process.

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