CLEAR

A 2x2 factorial randomised open label trial to determine the clinical and cost-effectiveness of hypertonic saline (HTS 6%) and carbocisteine for airway clearance versus usual care over 52 weeks in bronchiectasis

Protocol Number:	16178SE-AS
Protocol Version:	v6.0
Protocol date	07/07/2022
Protocol amendment number	5
EudraCT Number:	2017-000664-14
ISRCTN Number:	ISRCTN89040295
Sources of monetary or material support	
Funder	National Institute for Health Research Health Technology Assessment Programme Ref no. 15/100
Sponsor details	
Primary sponsor	Belfast Health and Social Care Trust
Ethics Reference Number:	17/NE/0339
Chief Investigator:	Professor Stuart Elborn School of Medicine, Dentistry and Biomedical Sciences Queen's University Belfast Wellcome-Wolfson Building 97 Lisburn Road Belfast BT9 7BL
Lead Applicant Physiotherapist:	Professor Judy Bradley School of Medicine, Dentistry and Biomedical Sciences Queen's University Belfast Northern Ireland Clinical Research Facility U Floor, Belfast City Hospital Lisburn Road Belfast BT9 7AB

FUNDED BY
NIHR | National Institute for Health and Care Research

PROTOCOL AUTHORISATION

Protocol Title	A 2x2 factorial randomised open label trial to determine the clinical and cost- effectiveness of hypertonic saline (HTS 6%) and carbocisteine for airway clearance versus usual care over 52 weeks in bronchiectasis
Protocol Acronym (if applicable)	CLEAR
Protocol Number	16178SE-AS
Protocol Version Number/Date	v5.0 09/06/2021
Protocol Amendments	v1.0 – v2.0 Removal of Examiner Blinding v2.0 – v3.0 Clarification of details included regarding visit 3 timing, internal pilot study timing and visit schedule V3.0-v4.0 Clarification of exclusion criteria, exacerbation management process and definition, spirometry data handling, sample size calculation and addition of spirometry sub-study protocol. V4.0 – 5.0 EME Sub Study(NIHR130192) added to protocol, amendment of inclusion criteria, sample size recalculation to 288 and removal of 2 year follow up for new patients. V5.0 – 6.0 Change to inclusion criteria; removal of SWATs A and B; addition of the collection of data from patient's electronic records at 104 weeks post randomisation; the addition of patient identification through G.P surgeries; and removal of the stipulation of 14 EME sites (to have no limit on the number of EME sites)

A review of the protocol has been completed and is understood and approved by the following:

Stuart Elborn	See attached email	DD / MM / YY YY
Chief Investigator	Signature	Date
Judy Bradley	See attached email	DD / MM / YYYY
Lead Applicant Physiotherapist	Signature	Date

Christina Campbell	See attached email	DD / MM / YYYY
Statistician	Signature	Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Full Wording
AE	Adverse Event
AR	Adverse Reaction
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BE	Bronchiectasis
BHSCT	Belfast Health and Social Care Trust
BTS	British Thoracic Society
CI	Chief Investigator
CF	Cystic Fibrosis
CRF	Case Report Form
CRN	Clinical Research Network
CTA	Clinical Trial Authorisations
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
EQ-5D-5L	EuroQoL five dimension five level questionnaire
EudraCT	European Clinical Trials Database
FEF	Forced Expiratory Flow
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HRCT	High Resolution Computed Tomography scan
HRQoL	Health-Related Quality of Life
HTA	Health and Technology Assessment Programme
HTS	Hypertonic Saline
IB	Investigator brochure
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISRCTN	International Standard Randomised Controlled Trial Number Register
MACRO	Clinical Trials Database
MHRA	Medicine and Healthcare Products Regulatory Agency
NICTU	Northern Ireland Clinical Trials Unit
NMB	Net Monetary Benefit
NIHR	National Institute for Health Research
PI	Principal Investigator
PICO	Population, Intervention, Comparison and Outcome(s)
PPI	Patient and Public Involvement
QALY	Quality adjusted life year
QoL-B	Quality of Life – Bronchiectasis
REC	Research Ethics Committee
RSI	Reference Safety Information
RSSQ	Respiratory and Systemic Symptoms Questionnaire
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SGRQ	Saint George's Respiratory Questionnaire

SPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study within a Trial
TMG	Trial Management Group
TSC	Trial Steering Committee
WTP	Willingness to Pay

1 STUDY SUMMARY

Scientific title	A 2x2 factorial randomised open label trial to determine the clinical and cost- effectiveness of hypertonic saline (HTS) 6% and carbocisteine for airway clearance versus usual care over 52 weeks in bronchiectasis
Public title	A study to compare the effect of two medications; hypertonic saline (HTS) and carbocisteine with routine care in helping to clear sputum in people with bronchiectasis
Health condition or problem studied	Bronchiectasis (BE)
Study Design	Multicentre, 2x2 factorial randomised, open label trial
Study Aim and Objectives	<u>Primary objective</u> To determine whether HTS (6%) and/or carbocisteine reduces the mean number of exacerbations over 52 weeks post randomisation. <u>Secondary objectives</u> To determine whether HTS and/or carbocisteine: i. Improves disease specific health related quality of life (HRQoL) at 52 weeks ii. Reduce time to next exacerbation iii. Reduce number of days of antibiotics related to exacerbations over 52 weeks iv. Improve generic HRQoL v. Are acceptable from a patient satisfaction perspective at 52 weeks vi. Are associated with adverse events (AEs) vii. Improve lung function over 52 weeks To assess: viii. The cost-effectiveness of the four treatment options ix. Patient adherence to HTS and carbocisteine over 52 weeks and how this impacts on the overall results Sub-studies Aim: To compare the criteria in the EMBARC definition to the criteria of a modified Fuch's definition for diagnosing pulmonary exacerbations in BE patients. To explore the use of mySpiroSense for remote spirometry during periods of stability and at the start and end of exacerbations in BE patients. Studies within a Trial (SWATs) Aim

	To explore the effect of methods used to optimise recruitment and retention. CLEAR EME Sub Study Is the mechanism of action of hypertonic saline and/or carbocisteine in the treatment of patients with bronchiectasis due to a decrease in sputum viscoelasticity, inflammation and bacterial load? **Primary Objective:** The primary objective is to measure sputum viscosity (G') and elasticity (G'') (which combined give a single summary measure of sputum viscoelasticity called the yield stress, T_c) at the initial visit and 2 weeks following commencement of treatment with HS and/or CS. **Secondary Objectives:** 1). Measure sputum viscoelasticity (yield stress, T_c), at 8 weeks following commencement of treatment with HS and/or CS. 2). Evaluate sputum inflammation as measured by IL-6, IL-8 and 8-isoprostane levels at the initial visit, 2 and 8 weeks following commencement of treatment with HS and/or CS. 3). Evaluate sputum bacterial load/composition at the initial visit, 2 and 8 weeks following commencement of treatment with HS and/or CS. The overall aim of this study is to provide mechanistic insight into the action of HS and/or CS in bronchiectasis.
Study Intervention	Patients will be randomised to one of four groups: i. Intervention 1: Standard care and twice daily nebulised HTS (6%) over 52 weeks ii. Intervention 2: Standard care and carbocisteine (750 mg three times per day until visit 3* reducing to 750 mg two times per day) over 52 weeks iii. Intervention 3: Standard care and a combination of twice daily nebulised HTS (6%) and 750 mg of carbocisteine three times per day until visit 3* reducing to 750 mg twice per day) over 52 weeks iv. Control: standard care over 52 weeks *Visit 3 occurs 8 weeks (+/- 7 days) post the baseline assessment.

Primary Outcome	Number of exacerbations over 52 weeks post randomisation
Key Secondary Outcomes	i. Disease Specific HRQoL (respiratory symptoms domain of quality of life with BE (QoL B) at 52 weeks ii. Time to next exacerbation post randomisation iii. Number of days of antibiotics for exacerbations over 52 weeks iv. Generic HRQoL (EQ-ED-5L) v. Health Service use over 52 weeks vi. Quality Adjusted Life Years (QALY) over 52 weeks vii. Measurement of Health Impairment using the St. Georges Respiratory Questionnaire viii. Patient preferences for treatment ix. Adverse events over 52 weeks x. Lung function over 52 weeks xi. Adherence to HTS and carbocisteine over 52 weeks
Key Inclusion and Exclusion Criteria	Inclusion criteria i. Diagnosis of BE on high resolution computed tomography (HRCT)/computed tomography (CT) scans ii. BE must be the primary respiratory diagnosis ***iii.*** One or more pulmonary exacerbations in the last year requiring antibiotics.* iv. Production of daily sputum** v. Stable from a respiratory point view for 14 or more days before randomisation with no changes to treatment*** vi. Willing to continue any other existing chronic medication throughout the study vii. Female subjects must be either surgically sterile, postmenopausal or agree to use effective contraception during the treatment period of the trial * This can included patient reported exacerbations *** This includes patients who expectorate sputum on a daily basis and/or patients that expectorate sputum on most days but experience difficulty in expectoration on other days. Patients that regularly do not have sputum and do not require to expectorate regularly should not be included in the study.* **** This inclusion refers to chest treatment however some antibiotics (e.g. for a urinary tract infection (UTI) may have chest coverage and need to be considered.*

	Exclusion criteria i. Age <18 years old ii. Patients with cystic fibrosis (CF) iii. Patients with COPD as a primary respiratory diagnosis iv. Current smokers, female ex-smokers with greater than 20 pack years and male ex-smokers with greater than 25 pack years. v. Forced expiratory volume in one second (FEV_1) <30% vi. If being treated with long term macrolides or other long term antibiotic, on treatment for less than one month before joining study or planning to stop treatment within one month of joining the study[#] vii. Patients on regular isotonic saline[##] viii. Treatment with HTS, carbocisteine or any mucoactives within the past 30 days[###] ix. Known contraindication or intolerance to hypertonic saline or carbocisteine x. Hypersensitivity to any of the active ingredients or the excipients of carbocisteine xi. Active peptic ulceration xii. Any heredity galactose intolerance, the Lapp-Lactase deficiency or glucose-galactose malabsorption xiii. Patients unable to swallow oral capsules xiv. Women who are pregnant or lactating xv. Participation in other trials of investigational products within 30 days *[#] If a patient is currently prescribed long term macrolides or other long term antibiotic they must have had no change to their treatment within the 30 days prior to randomisation i.e. if they are prescribed macrolides on a seasonal basis they must not have stopped or started treatment within the 30 days prior to being randomised.* *[##] Short term use of isotonic saline for exacerbation management is not an exclusion criteria. In addition patients using isotonic saline as a mixer for colomycin or using saline nasal sprays are not excluded.* *[###] Patients who use HTS and/or carbocisteine very occasionally or PRN i.e. during an exacerbation and have not used within 30 days prior to randomisation are not excluded.*
Countries of Recruitment	Northern Ireland, England, Scotland and Wales
Study Setting	NHS Sites with access to a BE population
Target Sample Size	288
Study Duration	81 months

2 STUDY TEAM

Chief Investigator CLEAR	Professor Stuart Elborn, Queen's University Belfast
CLEAR Lead Applicant	Professor Judy Bradley, Queen's University Belfast
CLEAR Co-Investigators	Professor Michael Clarke, Queen's University Belfast
	Dr James Chalmers, University of Dundee
	Dr Michael Loebinger, Royal Brompton & Harefield NHS Foundation Trust
	Dr Brenda O'Neill, Ulster University
	Professor Danny McAuley, Queen's University Belfast
	Professor Adam Hill, Edinburgh Royal Infirmary
	Dr Jamie Duckers, Cardiff and Vale University Health Board
	Dr Mary Carroll, University Hospital Southampton NHS Foundation Trust
	Dr Anthony De Soyza, Newcastle University
	Ms Cliona McDowell, Northern Ireland Clinical Trials Unit
	Professor Alistair McGuire London School of Economics and Political Science
	Dr Ashley Agus, Northern Ireland Clinical Trials Unit
Chief Investigator EME Sub Study	Professor Cliff Taggart
Patient and Public Involvement (PPI) Representative	Mrs Fiona Copeland Chair of the Primary Ciliary Dyskinesia Family Support Group
Statistician	Ms Christina Campbell, Northern Ireland Clinical Trials Unit
Health Economist	Dr Ashley Agus, Northern Ireland Clinical Trials Unit
Clinical Trials Unit	Northern Ireland Clinical Trials Unit (NICTU) 7 Lennoxvale Belfast BT9 5BY
Primary Sponsor	Alison Murphy, Belfast Health and Social Care Trust Royal Hospitals, Grosvenor Road, Belfast, BT12 6BA
Primary Sponsor's Reference	16178SE-AS
Contact for public queries	Northern Ireland Clinical Trials Unit 7 Lennoxvale Belfast BT9 5BY T: +4428 9063 5794 E: info@nictu.hscni.net

Contact for scientific queries	CLEAR Professor Judy Bradley School of Medicine, Dentistry and Biomedical Sciences Queens University Belfast Northern Ireland Clinical Research Facility U Floor, Belfast City Hospital Lisburn Road Belfast BT9 7AB T: +4428 9504 7973 E: Judy.Bradley@qub.ac.uk EME Sub Study Professor Cliff Taggart Wellcome Wolfson Institute for Experimental Medicine Queens University Belfast 97 Lisburn Road Belfast BT9 7BL T: +4428 90976383 E: c.taggart@qub.ac.uk

3 BACKGROUND AND RATIONALE

3.1 Background Information

Bronchiectasis (BE) is caused by irreversible dilatation thickening and sac like formations in bronchial walls. BE not caused by CF has been considered an “orphan lung disease” due to perception that it was a rare disease (1). Greater numbers of patients are now diagnosed with BE with HRCT scans. Current estimates suggest 1 in 1000 people in the UK have BE (2). It is a debilitating illness with patients usually suffering from a persistent cough, chronic daily sputum expectoration, recurrent chest infections and a poor HRQoL (3, 4). BE has been shown to be associated with significant mortality that displays a year on year increase of up to 3% per annum. Morbidity is also high and UK hospitals admission data found that BE was the primary diagnosis in 1 in 1800 admissions, with a 7-fold increase reported in hospital bed days needed for treating BE in the last eight years (5).

Mucus hypersecretion is a clinical feature of BE. Airway mucosal infection and/or inflammation associated with these diseases often gives rise to inflammatory products, including neutrophil-derived DNA and filamentous actin, in addition to bacteria, apoptotic cells and cellular debris that may collectively increase mucus production and viscosity. Mucoactive drugs potentially increase the ability to expectorate sputum and/or decrease mucus hypersecretion. Many mucoactive drugs are currently available and can be classified according to their mechanism of action. Mucoactive medications include expectorants, mucoregulators, mucolytics and mucokinetics.

3.2 Rationale for the Study

The BTS guidelines (1) provide detail on the current standard of care for patients with BE and currently there is not enough evidence to recommend mucoactive agents as part of standard care. By developing our understanding of the specific effects of mucoactive agents, we may result in improved therapeutic use of these drugs. UK registry data demonstrates clearly that BE centres prescribe mucoactives but this is to a small proportion of the BE population and is not in line with current guidelines. Current guidelines both UK and elsewhere highlight the need for more research (1). There are no licenced medications in BE however a large number of clinical trials are currently ongoing in BE and so this situation is likely to change. This is balanced against clear evidence that adherence to therapies in BE is low and directly related to the number of prescribed medications. Furthermore, low adherence is linked to patient outcomes (6). Therefore, it is essential that only drugs demonstrated to be effective in BE should be recommended. In the proposed study one of the medications is an oral medication (carbocisteine) and the other is an inhaled medication (HTS 6%).

3.3 Rationale for the Interventions

The BTS (2012) audit (7) as well as data from EMBARC database confirms that HTS and carbocisteine are the two most commonly used mucoactive agents in BE, albeit they are only used inconsistently, in a very small percentage of the population. The documented use in BTS audit (7) and European datasets confirm that HTS and carbocisteine are acceptable to both patients and clinicians. But the evidence base for both is weak in BE. Consequently, this study will answer important clinical questions that will influence future practice. This study will allow us to ascertain the role of these agents in the management of patients; in essence if they are effective up to 80% of patients do not have access to effective treatments and conversely, if they are ineffective then up to 20% of patients are on ineffective treatments.

There have been multiple, single intervention/ cross over studies exploring the use of HTS in BE (8-10). There is only one long term (one year) randomised parallel group study exploring

the efficacy of HTS (6%) versus placebo on hospital admission (11). This study was inconclusive in determining if the 'no effect' result was accountable to the poor study design or a true lack of effect of HTS in mucus clearance. This study has high scientific rigour and will provide definitive evidence on the effects of HTS and carbocisteine on the side effects associated with BE.

The evidence base for carbocisteine is poor. A Cochrane review has evaluated the evidence base for other mucoactive agents in BE and concluded that for DNase there is no evidence of benefit and evidence is insufficient to permit evaluation of the routine use of other mucoactives for BE and robust longer-term trials are required. This contrasts to other respiratory conditions where the evidence base for HTS and also for other mucoactives such as carbocisteine is stronger (11-13). We have also searched clinical trial registers. There are no active studies focused on the questions proposed in the current study. Therefore, the lack of evidence, as well as no currently active studies that will answer the questions around the use of HTS (6%) and carbocisteine in the management of BE justifies that the proposed study is relevant and timely.

Using a factorial design, we will randomise patients to one of the four possible combinations of HTS and carbocisteine: HTS alone, carbocisteine alone, HTS and carbocisteine, usual care; allowing us to include all patients in the main analyses of the effects of using HTS and of using carbocisteine.

In addition, the current trial will use eFlow rapid nebuliser and eTrack controller (furthermore referred to as eFlow and eTrack) that is working effectively with a different clinical trial (in CF) ongoing that the CI and lead applicant are participating in. The eFlow can deliver HTS on average with 3.6 (0.7 SD) minutes with optimal mass median diameter (MMD) 4.2 µm (0.2 SD). The eTrack records data on nebuliser usage when attached to the eFlow. Details of the nebulisation session are transferred from the eTrack via Bluetooth to a Qualcomm Life 2Net Hub (furthermore referred to as the 'Hub') and subsequently to a secure cloud based platform. The eTrack and Hub are linked to each other for secure data communication. The inclusion of this technology will help us distinguish between apparently negative trial results and issues surrounding adherence. As part of the patient information about the trial, we will tell patients how the eFlow works and how it collects usage data. We will explain that no one will review the adherence data until the end of the treatment period.

3.4 Rationale for Comparator

Each of the sites delivers care according to the BTS guidelines for BE. As part of the baseline assessment we will clarify the following for each patient: usual airway clearance offered to patients and frequency of review- if a patient does not have a regular airway clearance regimen, they will be taught active cycle of breathing techniques.

4 STUDY AIM AND OBJECTIVES

4.1 Research Hypothesis

HTS (6%) and/or the oral mucolytic carbocisteine will result in better outcomes than usual care over 52 weeks in patients with BE.

4.2 Study Aim

To deliver a UK multicentre study that will determine the clinical and cost -effectiveness of hypertonic saline HTS (6%) and carbocisteine for airway clearance versus usual care over 52 weeks in BE using a 2x2 factorial randomised open label trial.

4.3 Study Objectives

4.3.1 Primary objective

The primary objective is to determine whether HTS (6%) and/or carbocisteine reduces the mean number of exacerbations over 52 weeks post randomisation.

4.3.2 Secondary objectives

To determine whether HTS and/or carbocisteine:

i. Improves disease specific HRQoL at 52 weeks
ii. Reduce time to next exacerbation
iii. Reduce number of days of antibiotics for exacerbations over 52 weeks
iv. Improve generic HRQoL
v. Are acceptable from a patient satisfaction perspective at 52 weeks
vi. Are associated with AEs
vii. Improve lung function

The study will also assess:

viii. The cost-effectiveness of the four treatment options
ix. Patient adherence to HTS and carbocisteine over 52 weeks and how this impacts on the overall results.

4.4 Sub-Studies Aim

The data obtained in the CLEAR trial will also be used to answer or validate further questions:

i. A sub-study will be included which aims to validate and measure the sensitivity of the EMBARC definition for exacerbations in bronchiectasis. The study will compare the criteria in the EMBARC definition to the criteria of a modified Fuch's definition for diagnosing pulmonary exacerbations in bronchiectasis patients. The sub study is described in detail in Appendix 2.
ii. A sub-study will be included which aims to explore the use of mySpiroSense for remote spirometry during periods of stability (weekly measurements and measurements on the morning of study visits) and at the start and end of exacerbations in an adult bronchiectasis population. The sub study is described in details in Appendix 3.An EME Sub study will be included which aims to measure sputum viscosity (G') and elasticity (G'') (which combined give a single summary measure of sputum viscoelasticity called the yield stress, T_c) at the initial visit and 2 weeks following commencement of

treatment with HS and/or CS. The overall aim of this study is to provide mechanistic insight into the action of HS and/or CS in bronchiectasis. The sub study details is described in appendix 5.

iii.

4.5 SWATs Aim

There will also be SWATs completed which aim to explore the effect of methods used to optimise recruitment and retention.

The SWATs are described in detail in Appendix 4.

4.6 EME Sub Study Aim

Primary Objective:

The primary objective is to measure sputum viscosity (G') and elasticity (G'') (which combined give a single summary measure of sputum viscoelasticity called the yield stress, T_c) at the initial visit and 2 weeks following commencement of treatment with HS and/or CS.

Secondary Objectives:

1). Measure sputum viscoelasticity (yield stress, T_c), at 8 weeks following commencement of treatment with HS and/or CS.
2). Evaluate sputum inflammation as measured by IL-6, IL-8 and 8-isoprostane levels at the initial visit, 2 and 8 weeks following commencement of treatment with HS and/or CS.
3). Evaluate sputum bacterial load/composition at the initial visit, 2 and 8 weeks following commencement of treatment with HS and/or CS.

The overall aim of this study is to provide mechanistic insight into the action of HS and/or CS in bronchiectasis

The EME sub study is described in detail in Appendix 5

5 STUDY DESIGN

5.1 Study Design

This is a multicentre, 2x2 factorial randomised open label trial in BE with a 12-month follow-up period.

In PICO terms:

Population:	Adults with a confirmed diagnosis on HRCT/CT of BE and one or more pulmonary exacerbations in the previous year requiring antibiotics.
.	
Intervention 1:	Standard care and twice daily nebulised HTS (6%) over 52 weeks.
Intervention 2:	Standard care and carbocisteine (750 mg three times per day until visit 3* reducing to 750 mg twice per day) over 52 weeks.
Intervention 3:	Standard care and combination of twice daily nebulised HTS (6%) and carbocisteine (750 mg three times per day until visit 3* reducing to 750 mg twice per day) over 52 weeks.
Comparator:	Standard care over 52 weeks.
Outcome:	Number of exacerbations over 52 weeks post randomisation.

*Visit 3 occurs 8 weeks (+/- 7 days) post the baseline assessment.

5.1.1 Internal pilot study

The main trial will be preceded by an 8-month internal pilot study in at least 10 sites and will follow the same processes described in the main trial. It is planned that the pilot will run during months 4-11 with a target recruitment of 60 patients. If recruitment of 60 patients occurs more quickly than anticipated, progression to the full trial may occur earlier at the discretion of the funder. The internal pilot will be used to confirm recruitment rates, protocol compliance and data collection.

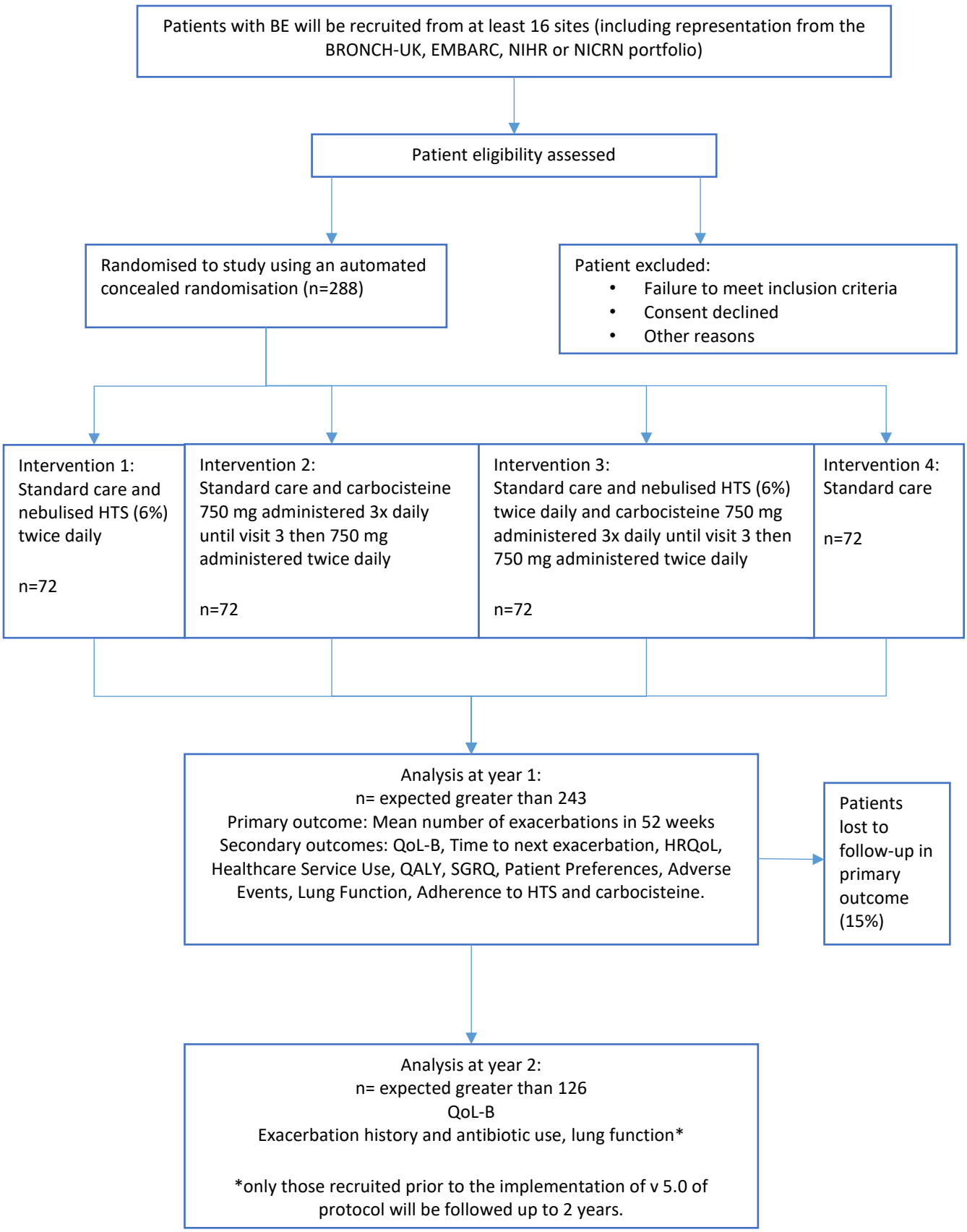
Recruitment rate will be used to determine whether progression to full trial continues. Our proposed progression criteria are:

i. 75-100% recruitment: progress to main trial following a review of screening logs at sites achieving less than 75%, an assessment of any barriers to recruitment at these sites, and the sharing of strategies from sites that are recruiting best
ii. 50-74% recruitment: progress to main trial following a review of screening logs and an assessment of any barriers to recruitment at all sites, and the sharing of strategies from sites that are recruiting best
iii. 25-49% recruitment: progress to main trial with a rescue plan developed by the Trial Steering Committee (TSC) and agreed with the NIHR HTA secretariat. This plan will likely include additional sites being recruited as well as a screening log and protocol / entry criteria review to instigate steps to ensure sample size is achieved
iv. Less than 25% recruitment: the trial will probably not progress. This STOP decision will be made by the TSC in association with the NIHR HTA secretariat

The pilot will also assess protocol compliance. This will be defined by evidence of quality and completeness of all datasets.

Participants enrolled in the pilot will be included in the analysis of the main study.

5.2 Study Schematic



5.3 Study Timeline

		2018						2019												2020				
Year		1												2										
Quarter		3			4			1			2			1			2			3			4	
Project Month		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
		J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M
Trial Stage	Pre-Grant Set-Up	Set up												Pilot								Main Study		
Finalise Protocol	X	X	X	X	X	X	X	X	X															
Ethics Approval					X	X	X	X	X	X	X													
MHRA Approval					X	X	X	X	X	X														
R&D Approvals									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial Set-up		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Identify/Recruit Staff		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Site Training						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pilot Study														X	X	X	X	X	X	X	X			
Main Study																						X	X	X
No of Sites														2	4	6	10	10	10	10	10	10	10	10
Patient Recruitment														1	2	6	4	10	8	14	12	10	5	10
Patient Accrual														1	3	9	13	23	31	45	57	67	72	82
Patient Follow-up																								
Management Meetings	XXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DMEC Meetings												X										X		
TSC Meetings					X																		X	
Data Analysis																								
Health Economics																								
Trial Publication																								

								2021												2022			
Year		3												4									
Quarter		1			2			3			4			1			2			3			4
Project Month	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46
	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A
Trial Stage																							
Finalise Protocol																							
Ethics Approval																							
MHRA Approval																							
R&D Approvals	X	X	X	X	X	X	X	X	X	X													
Trial Set-up	X	X	X	X	X	X	X	X	X	X													
Identify/Recruit Staff	X	X	X	X	X	X	X	X	X	X													
Site Training	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pilot Study																							
Main Study	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
No of Sites	11	12	13	13	13	13	14	14	14	14	14	14	14	14	14	14	24	24	24	24	24	24	24
Patient Recruitment	10	10	10	4	9	8	3	9	3	3	0	0	0	0	0	0	12	12	12	12	12	12	12
Patient Accrual	92	102	108	112	121	129	132	143	146	149	149	149	149	149	149	149	161	173	185	197	209	221	233
Patient Follow-up	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Management Meetings	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DMEC Meetings									X												X		
TSC Meetings										X												X	
Data Analysis																							
Health Economics																							
Trial Publication																							

									2023												2024		
Year			5												6								
Quarter			1			2			3			4			1			2			3		
Project Month	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69
	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M
Trial Stage						1 Year Follow Up												Analysis and Reporting					
Finalise Protocol																							
Ethics Approval																							
MHRA Approval																							
R&D Approvals																							
Trial Set-up																							
Identify/Recruit Staff																							
Site Training	X	X	X																				
Pilot Study																							
Main Study	X	X	X	X	X																		
No of Sites	24	24	24	24	24																		
Patient Recruitment	12	12	12	12	12																		
Patient Accrual	245	257	269	281	293																		
Patient Follow-up	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Management Meetings	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
DMEC Meetings										X													X
TSC Meetings											X												X
Data Analysis																		X	X	X	X	X	X
Health Economics																		X	X	X	X	X	X
Trial Publication																							X

5.4 End of Study

For the purposes of submitting the end of trial notification to the Sponsor, Medicines and Healthcare Products Regulatory Agency (MHRA) and Research Ethics Committee (REC) the end of the trial will be considered to be when database lock occurs for the final analysis. The trial will be stopped prematurely if:

- Mandated by REC
- Mandated by MHRA
- Mandated by the Sponsor (e.g. following recommendations from the DMEC)
- Funding for the trial ceases.

The REC that originally gave a favourable opinion of the trial and the MHRA who issued the Clinical Trial Authorisation (CTA) will be notified in writing once the trial has been concluded or if terminated early.

6 OUTCOMES

6.1 Outcome Measures

6.1.1 Primary Outcome Measure

Mean number of exacerbations over 52 weeks

6.1.2 Secondary Outcome Measures

i. Disease specific HRQoL (respiratory symptoms of domain of QoL-B) at 52 weeks
ii. Time to next exacerbation post randomisation
iii. Number of days of antibiotics related to exacerbations over 52 weeks
iv. Generic HRQoL
v. Health Service use over 52 weeks
vi. QALY over 52 weeks
vii. Measurement of health impairment using the SGRQ
viii. Patient preferences for treatment
ix. Adverse Events over 52 weeks
x. Lung function over 52 weeks
xi. Adherence to HTS and carbocisteine over 52 weeks

7 STUDY SETTING & PATIENT ELIGIBILITY

7.1 Study Setting

At least 16 NHS sites with access to a BE population managed according to BTS guidelines to ensure consistency of standard (usual care) across sites. Sites will include those which are part of the Bronch-UK/EMBARC research network, and if required additional sites will be chosen from the Northern Ireland Clinical research Network (NICRN)/National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio with preference given to sites with a proven track record of successful participation in clinical trials. A list of the study sites will be maintained in the TMF.

Patients recruited will undergo study visits in clinical research facilities (CRFs) or appropriate research areas within the outpatient setting. In exceptional circumstances, remote visits can be carried out if there is a risk to the patient to attend the facility. The CLEAR Guideline: Covering Remote Visits for Other Sites will be followed.

Staff must demonstrate and document a willingness to comply with the protocol, standard operating procedures, trial specific procedures, the principles of Good Clinical Practice (GCP) and regulatory requirements and be prepared to participate in trial-specific training.

7.2 Eligibility Criteria

Patients will need to be assessed using the inclusion and exclusion criteria as set out below. Eligibility to participate in the trial will be confirmed by a medically qualified person who is named on the delegation log.

Patients will be eligible to participate in the study if they fulfil the following criteria:

7.2.1 Inclusion criteria

i. Diagnosis of BE on CT/HRCT
ii. BE must be the primary respiratory diagnosis
iii. One or more pulmonary exacerbations in the last year requiring antibiotics*
iv. Production of daily sputum**
v. Stable from a respiratory point of view for 14 or more days before randomisation with no changes to treatment***
vi. Willing to continue any other existing chronic medication through the study
vii. Female subjects must be either surgically sterile, postmenopausal or agree to use effective contraception during the treatment period of the trial

** This can include patient reported exacerbations*

*** This includes patients who expectorate sputum on a daily basis and/or patients that expectorate sputum on most days but experience difficulty in expectoration on other days. Patients that regularly do not have sputum and do not require to expectorate regularly should not be included in the study.*

**** This inclusion refers to chest treatment however some antibiotics (e.g. for a urinary tract infection (UTI) may have chest coverage and need to be considered.*

7.2.2 Exclusion criteria

i. Age < 18 years' old
ii. Patients with CF

iii. Patients with COPD as a primary respiratory diagnosis
iv. Current smokers, female ex-smokers with greater than 20 pack years and male ex-smokers with greater than 25 pack years
v. FEV1<30%
vi. If being treated with long term macrolides or other long term antibiotic, on treatment for less than 1 month before joining study or planning to stop treatment within one month of joining the study[#]
vii. Patients on regular isotonic saline[##]
viii. Treatment with HTS, carbocisteine or any mucoactives within the past 30 days[###]
ix. Known intolerance or contraindication to HTS or carbocisteine.
x. Hypersensitivity to any of the active ingredients or the excipients of carbocisteine
xi. Active peptic ulceration
xii. Any heredity galactose intolerance, the Lapp-Lactase deficiency or glucose-galactose malabsorption.
xiii. Patients unable to swallow oral capsules.
xiv. Women who are pregnant or lactating
xv. Participation in another Clinical Trial of an Investigational Product within 30 days

[#] If a patient is currently prescribed long term macrolides or other long term antibiotic they must have had no change to their treatment within the 30 days prior to randomisation i.e. if they are prescribed macrolides on a seasonal basis they must not have stopped or started treatment within the 30 days prior to being randomised.

[##] Short term use of isotonic saline for exacerbation management is not an exclusion criteria. In addition patients using isotonic saline as a mixer for colomycin or using saline nasal sprays are not excluded.

[###] Patients who use HTS and/or carbocisteine very occasionally or PRN i.e. during an exacerbation and have not used within 30 days prior to randomisation are not excluded.

7.2.3 Co-enrolment guidelines

Patients enrolled in other investigational drug studies are not potential candidates for this study.

Patients enrolled in other observational studies are potential candidates for this study. This is at the PI's discretion.

EMBARC and BRONCH-UK are research studies currently ongoing across centres in the UK and Europe who manage patients with BE. These studies have been reviewed and approved by Research Ethics Committees in the UK. In order to collect 104-week follow-up data for patients enrolled on the trial it is planned to use data already available in the EMBARC or BRONCH-UK registries.

A large proportion of the potential participants for the trial may already be enrolled in the EMBARC or BRONCH-UK research studies. For these patients we will ask the patient for their consent to use their registry data for follow-up. Data from the registry at a time point closest to the planned 104-week follow-up time point for the patient will be used.

If a potential participant in the CLEAR trial is not already taking part in the EMBARC or BRONCH-UK research studies they will be asked to also consent and enrol in the BRONCH-UK or EMBARC studies by the local research team involved in these studies.

If the research team at the site are not involved in the BRONCH-UK or EMBARC research studies or if a patient is unwilling to consent to either of these studies, then we would collect the 104 week follow-up data required by the CLEAR during a study visit with the patient. Data can also be collected from patient's electronic records at 104 weeks post randomisation.

8 PATIENT SCREENING, CONSENT & RECRUITMENT

8.1 Recruitment

8.1.1 Screening procedure

Sites will screen BE clinics for potential eligible patients and will follow-up patients from pre-screening through to recruitment/decline to participate. Potential participants may be identified through patient electronic databases at each of the participating centres, through referrals or while in clinics. Potential participants may also be identified through electronic databases at specified G.P. surgeries with approvals in place to do so. In this case the suitable individuals will be sent a letter from the G.P. containing contact details of the local participating site. Sites will maintain screening logs that will include data on the numbers of patients meeting inclusion criteria for the trial but not entered into the trial and if applicable reasons for non-enrolment. Regular contact with each site by the coordinating centre will ensure that these logs are kept up to date. Recording this information is required to establish an unbiased study population and for reporting according to the CONSORT statement (14).

8.1.2 Informed consent procedure

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It is the responsibility of the Principal Investigator (PI) (or designee) to ensure that written informed consent/advice is obtained from each participant (or a legal representative) prior to entry into the trial and completing any study specific procedures. The Investigator (or designee) taking informed consent must be GCP trained, suitably qualified and experienced and have been delegated this duty by the PI on the delegation log.

All interested individuals who are determined as being eligible using the screening criteria will be provided with a participant information sheet to read thoroughly and will be given as much time as necessary to consider the study fully before being contacted by a member of the research team to ascertain if they are happy to take part. If required, the research team can schedule an appointment for the potential participant to attend for further discussion before consent is obtained. Throughout this time the potential participant will be given opportunity to ask questions. Where participants require further clarification about the benefits and risks of participating, this will be provided by the research team.

When the potential participant confirms they are happy to participate, written informed consent will be obtained by an appropriately trained research nurse and medically trained investigators who will be supported in this by both a PI and other local infrastructure at each site. A copy of the signed informed consent form will be given to the subject. The original shall be kept by the PI in the Investigator site file at each research site and a copy filed in the patient's medical notes. Once randomised the participant's GP will be informed by letter of their participation in the study. If a potential participant declines to give consent, their details will be recorded by the relevant research coordinators assigned to the study to ensure that they won't be inadvertently re-invited to participate in the study.

If a potential participant is currently prescribed HTS, carbocisteine or other mucoactives for the treatment of their BE and the patient wants to be part of the trial, the potential participant and physician may decide to discontinue their current treatment in order to be able to participate. Informed consent should be taken and the baseline visit/confirmation of eligibility completed at least 30 days after the patient has started a washout from HTS, carbocisteine or other mucoactive.

If a patient is currently prescribed long term macrolides or other long term antibiotic they must have had no change to their treatment within the 30 days prior to randomisation i.e. if they are prescribed macrolides on a seasonal basis they must not have stopped or started treatment within the 30 days prior to being randomised.

Where the patient has provided written consent in advance of the baseline study visit the study team will review with the participant at the start of the visit and ensure ongoing consent prior to completing any study specific procedures.

8.1.3 Withdrawal of consent

Potential participants will be made aware by the participant information sheet, and at time of consent, that they have the right to withdraw from the study at any point without giving any reason, and without it affecting in any way their future medical care.

Patients may withdraw or be withdrawn from the trial at any time without prejudice and consent will be requested to use the data collected to that point. If a participant withdraws from any intervention they will asked to be followed-up as part of the trial.

- If the participant withdraws during year 1, they will be asked to attend follow up visits for collection of outcome data. If they do not wish to attend outcome data collection, then permission will be sought to access medical notes for collection of data related to the trial e.g. the use of antibiotics.
- If the participant withdraws consent during year 2 of the trial, then we will request permission to use their trial data within the main analysis and for access to their medical notes for the collection of relevant data for year 2 of follow up.

In the event that the participant requests to withdraw from all parts of the study, only anonymised data recorded up to the point of withdrawal will be included in the study analysis.

Participants may be withdrawn from the study at the discretion of the Investigator due to safety concerns.

9 ASSIGNMENT OF INTERVENTIONS

9.1 Interventions

9.1.1 Intervention description

Intervention 1:	Standard care and twice daily nebulised HTS (6%) over 52 weeks:
Intervention 2:	Standard care and carbocisteine (750 mg three times per day until visit 3 reducing to 750 mg two times per day) over 52 weeks.
Intervention 3:	Standard care and combination of twice daily nebulised HTS (6%) and carbocisteine (750 mg of three times per day until visit 3 reducing to 750 mg twice per day) over 52 weeks.
Control:	Standard care over 52 weeks.

Intervention will be reported according to Tidier checklist (15).

Patients on the standard care arm will use airway clearance techniques in the management of their BE.

After 52 weeks all patients will revert to standard care and patients may/may not be prescribed an oral/nebulised mucoactive.

9.1.2 Assignment of Intervention

Randomisation will be completed by an appropriately trained and delegated member of the research team.

When the research team at each study site identifies a patient suitable for enrolment, they will obtain informed consent for participation in the trial. The randomisation service will allocate a unique trial identifier to each patient in accordance with the study randomisation schedule prepared prior to the start of the trial. The unique identifier allocated at the time of randomisation will be used throughout the trial for purposes of patient identification.

Treatment allocation will be assigned using an automated randomisation process that each site research team will complete. Eligible participants will be allocated to one of the four treatment groups (three intervention groups or one standard care group) in a 1:1:1:1 ratio using a central randomisation system. Randomisation will be stratified by site, to minimise baseline imbalances in antibiotic use due to exacerbations in the last year (2-3 times, >3times) and based on current use of macrolides (yes, no).

10 STUDY DRUG

10.1 Study Drug Supply and Packaging

The following are regarded as investigational medicinal products for the purposes of this study:

- Carbocisteine 375 mg capsules
- HTS 6% - Mucoclear® 4 mL ampoules – Sodium Chloride inhalation solution 60 mg per 1 mL

Carbocisteine 375 mg is a commercially available UK licensed medicine, which will be sourced by local site pharmacies.

MucoClear 6% is a CE-marked medical product manufactured by Pari Pharma. The manufacturer will provide commercial stock of Mucoclear for use in the study. Participating site pharmacies will order directly from the manufacturer as detailed in the study specific IMP guideline.

10.2 Study Drug Prescribing, Labelling and Dispensing

At the baseline visit when a patient is recruited an authorised member of the research team will contact the randomisation service to obtain the unique trial identifier and the treatment allocation assigned to the participant. The investigator will complete and sign a trial prescription form detailing the unique trial identifier and the treatment assigned and this will be presented to the pharmacy. The randomisation service will send a confirmation email to the site pharmacy confirming the assigned treatment group along with the corresponding unique trial identifier for the patient.

At the time of dispensing, carbocisteine and/or HTS 6% will be labelled by the site pharmacist according to local procedures and applicable regulatory requirements for investigational medicinal products.

Study medication will also be dispensed at visits 3 and visit 4. The investigator will complete and sign a trial prescription detailing the unique trial identifier and the treatment assigned and this will be presented to the pharmacy. Sufficient quantities of whole commercial packs will be dispensed to cover the interval between dispensing visits.

There is the option for visits to be delivered remotely. If visits are remote, the study drug should be dispensed as outlined in the IMP visit schedule **and collection/delivery arranged** with the patient. Further details are provided in the study specific IMP guidelines.

10.3 Treatment Regimen and Administration

Standard care is the use of various airway clearance techniques for the management of BE.

On the standard care arm and the treatment arms continuing standard care, participants will receive advice on airway clearance. If they are not familiar with an airway clearance technique they will be taught the active cycle of breathing techniques.

Participants allocated to the standard care and HTS 6% arm will be instructed to administer a 1 x 4 mL ampoule twice daily for 52 weeks using the eFlow provided by their local study team. The participant will be educated on cleaning and usage of the eFlow during their baseline visit and subsequent visits. Participants will also continue to adopt standard care airway clearance techniques throughout the treatment period.

Participants allocated to the standard care and carbocisteine arm will be instructed to take 2 x 375 mg capsules three times daily. At visit 3 they will then be instructed to reduce their dose to 2 x 375 mg capsules twice daily for the remainder of the 52 weeks. Participants will also continue to adopt standard care airway clearance techniques throughout the treatment period.

Participants allocated to the standard care and combination of HTS 6% and carbocisteine arm will be will be instructed to administer a 1 x 4 mL ampoule twice daily for 52 weeks using the eFlow provided by their local study team. They will also be instructed to take 2 x 375 mg capsules three times daily. At visit 3 they will be instructed to reduce their dose to 2 x 375 mg capsules twice daily for the remainder of the 52 weeks. Participants will also continue to adopt standard care airway clearance techniques throughout the treatment period.

The dosing regimen for carbocisteine is in accordance with the Summary of Product Characteristics. The dosing regimen for HTS 6% is in accordance with the patient information leaflet for the product.

All participants will receive an Airway Clearance Record/Action Plan as a reminder of the treatment regimen. Study staff will review this with the participant at each study visit and update it as required.

10.4 Drug Response Assessment

All patients allocated to a treatment group including HTS 6 % will complete a drug response assessment with the MucoClear 6% in accordance with the study specific guideline. In the rare event that a patient fails their drug response assessment and is unable to be reassessed on the same day then the prescribed medication for the patient should be returned to pharmacy and a further visit arranged to repeat the drug response assessment and any remaining assessments from the baseline visit. If a patient needs to be reassessed, consideration should be given to using a pre-test bronchodilator. If a bronchodilator is required to enable a patient to pass a re-test the patient should be prescribed bronchodilator for use during the study treatment period. They will be prescribed salbutamol 100mcg, 2 puffs twice daily prior to each administration of HTS 6% for the duration of the study treatment period.

10.5 Study Drug Accountability, Compliance and Adherence

The site pharmacist will be responsible for maintaining records of the disposition of all study drugs dispensed, unused/expired, returned to pharmacy and destroyed. A study-specific drug accountability form will be used.

Participants will be asked to store the medication according to the manufacturer's instructions.

Patients will be asked to return any unused carbocisteine and/or HTS 6% ampoules at their next study visit. Site staff will confirm with patients if they took their medication as prescribed and will record details of any missed doses the patient's records. Used ampoules of HTS 6% will not be returned as adherence data will be obtained from the PARI eTrack.

The study drugs will not be destroyed until authorised by the CTU.

Adherence to HTS will be monitored utilising the PARI eTrack. The eTrack records data on the nebulisation session when attached to the eFlow. When the eTrack is paired and in proximity to the Hub encrypted data is transmitted via Bluetooth to the Hub and then onward to a secure cloud based platform. As part of the patient information about the trial, the participant will be provided with an explanation on how the eFlow and eTrack work and how

usage data is collected. Each patient will be provided with an eTrack base unit, which they will connect to their eFlow at each nebulisation. They will be instructed bring their eFlow and eTrack with them to every study visit.

During each study visit the site staff will transmit the adherence data from the eTrack to the Hub held at the site via Bluetooth, before returning the units to the patient. Encrypted data will be transmitted from the hub to the secure cloud platform where the data will be stored and can be accessed and viewed by the local research team at each site for their patients and by the CTU and/or CI for all patients.

It will be explained to the participant that their usage data will not be reviewed until the end of the 52 week treatment period. This adherence data will be used to help understand the results more fully and provide us a basis to improve understanding of patient behaviours with regard to nebulised therapy. Adherence data will be reviewed with the patient during the 52-week study visit.

10.6 Treatment Discontinuation

Participants may withdraw from treatment at any time, without providing an explanation, or if discontinuation is considered by the medical team to be in the best interests of the patient. Reasons for withdrawal may include:

- Intercurrent significant illness
- Occurrence of intolerable side effects
- Patient request
- Protocol violations or non-compliance as determined by the PI
- Decision by the PI that the study drug should be discontinued on safety grounds
- Complexity of study
- Increased hypertonic intolerance
- Adverse Event or Serious Adverse Event

The reason for discontinuation of treatment should be recorded on the CRF and any unused medication returned to pharmacy.

Adherence to usual care at the research sites will be monitored throughout the study and as a preventative measure the trial management group will highlight and review any site that begins prescribing HTS or carbocisteine as part of usual care.

10.7 End of Study Drug

Following the completion of the 52 week treatment period, the participant may request to continue treatment if there has been a perceived benefit from participating in the study. In such instances, the patient should discuss this with the clinician in charge of their care.

10.8 Concomitant Therapy

Any prescribed medication deemed necessary to provide adequate medical care to the patient is permitted, other than as stated in the study exclusion criteria. Caution is recommended for the use of carbocisteine in those with a history of gastroduodenal ulcers, or those taking concomitant medications known to cause gastrointestinal bleeding. Patients will be asked about all medications taken prior to entry into the study and at each study visit. If patients report any new or change in frequency/severity of GI symptoms, the PI should consider if carbocisteine should be discontinued on safety grounds.

11 STUDY ASSESSMENTS & PROCEDURES

11.1 Schedule of Assessments

All patients must be evaluated during the study according to the schedule of assessments outlined in below.

Study Visit Number		1	2*	3*	4*	5*	6*~+
Visit Schedule	Prior to entry	Base-line	Week 2	Week 8	Week 26	Week 52	Week 104
Visit Window		+ 14 days	+/- 3 days	+/- 7 days	+/- 14 days	+/- 14 days	+/- 14 days
Assessments							
Inclusion & Exclusion Criteria Review	x						
Informed consent	x						
Review Informed consent (if applicable)		x					
Demographics		x					
Patient BE Characteristics		x					
Assess Sputum colour from sample, if avaliable		x					
Patient Standard Care Review		x					
Medical History		x					
Review Medications		x	x	x	x	x	
Vital Signs		x	x	x	x	x	
Urine Pregnancy Test		x					
Physical Exam		x					
Confirmation of Eligibility		x					
Adverse Events		<----------				---------->	
Respiratory and Systemic Symptoms Questionnaire (RSSQ) &		x	x	x	x	x	
Exacerbation/Antibiotic Use^			x	x	x	x	x
EME Sub Study							
Measure sputum elasticity (G') and viscosity (G'') (which combined represent the yield stress, T_c)		X	X				
EME Secondary Objectives							
Measure sputum elasticity (G') and viscosity (G'') (which combined represent the yield stress, T_c)				X			
Evaluate sputum inflammation as measured by IL-6, IL-8 and 8-isoprostane levels		X	X	X			
Evaluate sputum bacterial load/composition		X	X	X			
Patient Questionnaires							
Treatment Satisfaction Questionnaire			x	x	x	x	
QoL-B		x	x	x	x	x	x
SGRQ		x	x	x	x	x	

EQ-5D-5L		x	x	x	x	x	
Health Service Use Questionnaire		x	x	x	x	x	
Lung Function Tests		x	x	x	x	x	x
Randomisation & Treatment Allocation		x					
IMP prescribing & Dispensing		x		x	x		
Drug response assessment (for patients assigned any HTS group)		x					
Airway Clearance Record/Action Plan		x	x	x	x		
Patient Training on Usual care, spirometers and eFlow		x	x	x	x		
eFlow/mySpirosense Utility Questionnaire						x	
Spirometry (at home)[#]		<---------->					
Exacerbation Management^ Review duration, symptoms & antibiotic use Review spirometry RSSQ Review with Investigator or Designee		<----------> <----------> <----------> <----------> <---------->					

**Week 2-104 study visit schedule will be based on the completion of all Baseline study activities, when baseline activities occur over a number of different days.*

~It is planned that this data will be collected from the EMBARC or BRONCH-UK Registry. If this is not possible the participant will be asked to visit the research site for the data to be collected.

[&] *If a participant's scheduled study visit corresponds with the start or end of an exacerbation the RSSQ that links to the exacerbation should be completed i.e. if it is the start of an exacerbation complete the RSSQ (symptoms of exacerbation version) instead of RSSQ (since last visit version). If it is at the end of an exacerbation complete the RSSQ (end of exacerbation version) instead of RSSQ (since last visit version). If the scheduled study visit falls in the middle of an exacerbation complete the RSSQ (since last visit version).*

^The start date, associated symptoms, end dates (when symptoms resolved) and details of any antibiotics taken will be recorded. Data may be collected by telephone or during an unscheduled visit.

[#]*Patients will be asked to complete spirometry at home on a weekly basis using the handheld spirometers provided. During weeks with study visits 2-5, the spirometry should be completed on the morning of their study visit.*

+ Visit 6 at 104 weeks will only be completed for those patients recruited prior to the implementation of protocol v5.0. Those recruited after this will complete the study after visit 5 at 52 weeks.

11.2 Study Visits and Procedures

All study assessments and procedures for a participant will be performed by delegated members of the research team. If a patient requires a separate visit for a repeat Drug response assessment they will then complete any remaining baseline assessments. Their subsequent study visits (2-6) will be scheduled at time-points relative to this visit. The activities to be completed at each of the study visits are detailed below:

Visit 1: Baseline Visit

- Review of Inclusion/Exclusion Criteria and confirmation of eligibility *(prior to entry or at start of baseline visit)*
- Informed Consent *(prior to entry or at start of baseline visit)*
- Demographic Information (date of birth, gender, ethnicity, smoking status, e-cigarette and pipe usage)
- Patient BE Characteristics (Date of CT/HRCT scan and radiological severity/Exacerbation and Antibiotic History/mMRC Breathlessness score/Sputum Colonisation/Sputum Colour from sample if available)
- Review details of patient standard care for BE (e.g. airway clearance techniques) as applicable)
- Medical History
- Medications
- Vital Signs (height, weight, temperature, BP, Pulse, RR, SpO2)
- Urine Pregnancy Test
- Physical Examination
- Recording and reporting of AEs
- RSSQ
- Questionnaires (QOL-B, SGRQ and EQ-5D-5L)
- Health Service Use Questionnaire
- Issue Health Service Use Log (0-2 weeks)
- Lung function tests (review bronchodilator use, time of spirometry, FEV_1, FVC, FEF_{25-75}) and FEV1% predicted
- Randomisation and treatment allocation
- Prescribing and dispensing of treatments (if applicable)
- Drug response assessment (if applicable)
- Provision of eFlow and training on use and cleaning (if applicable)
- Training in standard care airway clearance techniques as applicable
- Airway Clearance Record/Action Plan
- Provision of spirometers and training on use of spirometers
- Collect EME sputum sample

Visit 2: Week 2 (+/- 3 days)

- Review medications
- Vital Signs (weight, temperature, BP, Pulse, RR, SpO2)
- Treatment Satisfaction Questionnaire (if applicable)
- Recording and reporting of AEs
- RSSQ
- Review exacerbations and antibiotic use
- Questionnaires (QoL-B, SGRQ and EQ-5D-5L)
- Health Service Use Questionnaire (2 week) using Health Service Use Log (0-2 weeks)
- Issue Health Service Use Log (2-8 weeks)

- Lung function tests (review bronchodilator use, time of spirometry, FEV_1, FVC, FEF_{25-75}) and FEV1% predicted
- Review instructions for use of eFlow including cleaning (if applicable)
- Review/Update Airway Clearance Record/Action Plan (if applicable)
- Review instructions for use of spirometers
- Collect EME sputum sample

Visit 3: Week 8 (+/- 7days)

- Review Medications
- Vital Signs (weight, temperature, BP, Pulse, RR, SpO2)
- Treatment Satisfaction Questionnaire (if applicable)
- Recording and reporting of AEs
- RSSQ
- Review exacerbations and antibiotic use
- Compliance to Intervention (if applicable)
- Questionnaires (QoL-B, SGRQ and EQ-5D-5L)
- Health Service Use Questionnaire (8 week) using Health Service Use Log (2-8 weeks)
- Issue Health Service Use Log (8-26 weeks)
- Lung function tests (review bronchodilator use, time of spirometry, FEV_1, FVC, FEF_{25-75}) and FEV1% predicted
- Prescribing and dispensing of treatments (if applicable)
- Review instructions for use of eFlow including cleaning (if applicable)
- Review/Update Airway Clearance Record/Action Plan (if applicable)
- Review instructions for use of spirometers
  Collect EME sputum sample

Visit 4: Week 26 (+/- 14 days)

- Review Medications
- Vital Signs (weight, temperature, BP, Pulse, RR, SpO2)
- Treatment Satisfaction Questionnaire (if applicable)
- Recording and reporting of AEs
- RSSQ
- Review exacerbations and antibiotic use
- Compliance to Intervention (if applicable)
- Questionnaires (QOL-B, SGRQ, and EQ-5D-5L)
- Health Service Use Questionnaire (26 weeks) using Health Service Use Log (8-26 weeks)
- Issue Health Service Use Log (26-52 weeks)
- Lung function tests (review bronchodilator use, time of spirometry, FEV_1, FVC, FEF_{25-75}) and FEV1% predicted
- Prescribing and dispensing of treatments (if applicable)
- Review instructions for use of eFlow including cleaning (if applicable)
- Review/Update Airway Clearance Record/Action Plan (if applicable)
- Review instruction for use of spirometers

Visit 5: Week 52 (+/- 14 days)

- Review Medications
- Vital Signs (weight, temperature, BP, Pulse, RR, SpO2)
- Treatment Satisfaction Questionnaire (if applicable)

- Recording and reporting of AEs
- RSSQ
- Review exacerbations and antibiotic use
- Compliance to Intervention (if applicable)
- Questionnaires (QOL-B, SGRQ, and EQ-5D-5L)
- Health Service Use Questionnaire (52 weeks) using Health Service Use Log (26-52 weeks)
- Lung function tests (review bronchodilator use, time of spirometry, FEV_1, FVC, FEF_{25-75}) and FEV1% predicted
- Review eFlow adherence data
- Treatment plan for Year 2
- Eflow/myspiroSense Utility Questionnaire

Week 104 Follow-up

It is planned that this data will be collected from the EMBARC or BRONCH-UK Registry. If this is not possible the participant will be asked to visit the research site for the data to be collected or collected from the patient's electronic records*.*

- Review exacerbations and antibiotic use
- Questionnaires (QOL-B)
- Lung function tests (date and time of spirometry, FEV_1, FVC)

Please note: *Visit 6 at 104 weeks will only be completed for those patients recruited prior to the implementation of protocol v5.0.*

The quality of life questionnaires (QOL-B, SGRQ and EQ-5D-5L) and the health service use questionnaire will be completed independently and prior to completing any other study assessments at each time point. Patients will be provided with health service use logs to record information following their baseline visits until visit 5. Patients will use these logs as reference to complete their health Service Use questionnaires at visits 2-5 to encourage independent completion. The questionnaires will be checked for missing responses only by the local research team and missing items pointed out to the patient to ensure completion.

Spirometry

The local research team will complete lung function tests at each study visit when the patient attends the research site. According to the study specific guidelines, they will complete spirometry using SpiroSensePro self-calibrating spirometers.

All patients will also be provided with a hand held self-calibrating spirometers (mySpiroSense) to complete regular lung function tests at home and if they experience symptoms or signs of an exacerbation. During weeks that the patient has study visits 2-5, they should complete their spirometry at home on the morning of the visit. The patient will be provided with a guidance document detailing how to use the spirometers and how to complete a lung function test. Sites may set up reminders for patients to conduct their weekly spirometry.

They will be asked to conduct spirometry (3 readings) around the same time of day (and where possible post morning airway clearance treatments) on a weekly basis. Patients will be asked to take all measurements at the same time point relative to when they take their medications i.e. bronchodilators etc. If the patient is unable to complete spirometry weekly this will not be recorded as a protocol deviation. The spirometry readings are retained in the memory of the device. Patients will be instructed to bring their spirometers to each study visit. The research staff will download any data before returning the spirometer to the patient.

Exacerbation Management

During the treatment period, patients will be asked to telephone the site if they feel they are experiencing symptoms of an exacerbation (i.e. symptoms greater than the day to day fluctuations in symptoms that a patient would normally experience and should ideally be persistent for at least 48 hours). Patients will be advised to wait at least 48 hours from the onset of signs/symptoms before contacting the study team.

Details of the exacerbations will be recorded by a member of the study team by telephone or during an unscheduled visit. Upon patient contact, a member of the study team will undertake the following:

- Identify the patient and what treatment group they are in.
- Complete the RSSQ questionnaire (symptoms of exacerbation version) with the patient.
- Note the date of the start of the symptoms.
- Ask the patient if they did a lung function test on that day and, if not, instruct them to do so using the mySpiroSense spirometer.
- Ask the patient about any new concomitant medications or airway clearance techniques prescribed and update the concomitant medication form and airway clearance technique log, if required.

The results of the RSSQ will be available immediately. After completing the above tasks, the member of the study team will use the RSSQ results to score the exacerbation in the patient's case report form (CRF) according to the EMBARC criteria then discuss the patient reported symptoms (and duration of symptoms) with Investigators or other physicians at the site who will determine whether a prescription for antibiotics is appropriate or any other change to the patient's treatment is required. Any such decision will be ultimately based on the clinical judgment of the responsible clinician.

If the patient has had symptoms for less than 48 hours and has not or is not to be started on any antibiotic treatment, a second follow up telephone call should be arranged with the patient at least 48 hours after the onset of their symptoms and the procedures above repeated. In the event symptoms are inconsistent with an exacerbation, and/or a face to face visit is required the patient may be asked to make an unscheduled study visit for further examination.

If an exacerbation is diagnosed, the member of the study team will undertake the following:

- Direct the prescription of antibiotics as instructed by the Investigator (type of antibiotic, dose and length of treatment). Arrangements for antibiotics may be directed in different ways depending on local procedures i.e. patients may be directed to commence prophylactic rescue packs held at home, a prescription may be obtained in consultation with their GP or other local arrangements may apply. If antibiotics are not prescribed, the reasons for not doing so should be recorded.
- Record information this alongside any changes in bronchiectasis treatment management on the CRF and concomitant medication form or the airway clearance technique log, if applicable.
- Schedule a follow-up telephone call with the patient to assess for the resolution of the exacerbation. The date for this will be determined by the end of any antibiotic course prescribed to the patient.

The potential end of the exacerbation is defined as the time when the prescribed antibiotic course is completed. At this time point (or up to 14 days later) a member of the study team will call to the patient and:

- Administer the RSSQ questionnaire (end of exacerbation version).

- Ask the patient to complete a lung function test using the mySpiroSense spirometer.
- Review the concomitant medication form and the airway clearance technique log.

The collection of follow-up symptoms will allow exploration of resolution of the exacerbation as well as provide validity of the diagnosis of the exacerbation. If the patient symptoms have not resolved discuss with the investigator who will determine whether a further prescription for antibiotics is required. If further antibiotics are prescribed, arrangements will be made to complete the call for resolution of an exacerbation at the end of their last course of antibiotics. The exacerbation will be counted as one event and the end of this will be when the last antibiotic course is completed.

In the case a patients arrives for a scheduled study visit and feels an exacerbation is imminent but didn't make contact with the site, a member of the study team will collect the information required regarding the exacerbation and the RSSQ questionnaire (symptoms of exacerbation version) will be administered during their visit. If a schedule study visit coincides with the end of the exacerbation the site will collect the information required and the RSSQ questionnaire (end of an exacerbation version) will be administered during their visit.

Many patients hold prophylactic antibiotics at home but will be directed and regularly reminded at each study visit to contact study staff when feeling signs/symptoms of an exacerbation. This will ensure that antibiotic prescription is directed and recorded through clinical staff.

However patients will be instructed that if they experience symptoms for at least 48 hours during the weekend on a bank holiday they should proceed with taking any rescue pack antibiotics or GP prescribed antibiotics and then report to site staff as soon as possible so that the details can be documented.

11.3 Study Instruments

Spirometry

The BTS guidelines for the management of BE state that spirometry and lung function should be measured in all patients with BE and that these measurements should be made at least annually. Measurements of lung function can give an indication of the degree of airflow obstruction and disease severity; it is hypothesised that the use of mucoactive agents may ease the degree of obstruction through improved sputum clearance and this will be evidenced through the lung function results at each time point. At each visit spirometry will be completed to determine FEV_1 and FVC. The FEV_1/FVC ratio will also be derived and FEV1 % predicted. will be calculated by the spirometer. FEF_{25-75} will also be completed at all visits except week 104. In addition, patients will be asked to complete spirometry at home on a weekly basis using hand held spirometer provided and at the beginning and end of any potential pulmonary exacerbation.

RSSQ

The RSSQ was created in order to have a harmonised approach for the identification of CF-related pulmonary exacerbations. A member of the research team will administer the questionnaire at each study visit. A specific script is used to capture changes in the predefined signs and symptoms relative to normal day to day fluctuations. 2 modified versions of the RSSQ will be used to capture details around potential exacerbations reported between study visits. To facilitate the completion of the modified RSSQ remotely, at the baseline visit patients will be provided with a diagram illustrating where the sinuses are located (Section 20.3.13.1). One of the modified versions will be used to ask patients about symptoms in the past 48 hours, when they have been feeling unwell for 48 hours and when they contact the site to report a possible pulmonary exacerbation. In addition, another modified version will be used to ask

patient about symptoms at the end of any reported exacerbations after they have been prescribed treatment or an antibiotic to treat the exacerbation. If a participant's scheduled study visit corresponds with the start or end of an exacerbation the RSSQ that links to the exacerbation should be completed i.e. if it is the start of an exacerbation complete the RSSQ (symptoms of exacerbation version) instead of RSSQ (since last visit version). If it is at the end of an exacerbation complete the RSSQ (end of exacerbation version) instead of RSSQ (since last visit version). If the scheduled study visit falls in the middle of an exacerbation complete the RSSQ (since last visit version).

QoL-B

The QoL-B assesses symptoms, functioning and health-related quality of life specific to patients with BE; it assesses eight different items including, respiratory symptoms, physical, role, emotional and social functioning, vitality, health perceptions and treatment burden. This questionnaire is reliable and valid (16-18).

SGRQ

SGRQ was designed to measure health impairment in people with COPD and asthma (4). It has been validated for use in the BE population (16). It is a two-part questionnaire; part 1 addresses the frequency of their respiratory symptoms, assessing the patients' perception of their respiratory problems in the past. Part 2 assesses the patients' current state in relation to their respiratory problems.

EQ-5D-5L

EQ-5D-5L is a validated questionnaire that is applicable to a wide range of health conditions it provides a simple descriptive profile and a single index value for health status that can be used in both clinical and healthy populations. It consists of two parts; part 1 is descriptive and consists of a visual analogue scale which records the respondent's self-rated health on a 20 cm vertical with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine' Part 2 is profile based on 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression) considered at 5 increasingly worsening levels. Published, validated tariff values can then be easily attached to the returned profiles to use as health state valuations in determining Quality Adjusted Life Years (QALY) gains (19).

Health Service Use Questionnaire

A questionnaire and log have been developed specifically for the CLEAR study to capture participant's health service use. Participants will be provided with the log at baseline, 2, 8 and 26 weeks to prospectively capture their service use and details of prescribed medications (including antibiotics). The questionnaires will be completed at the baselines, 2, 8, 26 and 52 week visits with reference to the logs. At the baseline participants will be asked to recall their use of the health service in the previous four weeks.

Treatment Satisfaction Questionnaire for Medication

Participants assigned to treatment groups with HTS and/or carbocisteine will complete a questionnaire at 2, 8, 26 and 52 weeks regarding how satisfied or dissatisfied they are with the medication they are taking in the trial. They will be asked what they think about the effectiveness, side effects, and convenience experienced when using the medication over the last two to three weeks, or since they last used it. Patients assigned to the treatment group taking both HTS and carbocisteine will be asked to complete separate questionnaires for each treatment and will always complete the questionnaire for HTS first to ensure a standardised order of completion.

12 DATA MANAGEMENT

12.1 Data Quality

Data integrity and study credibility depend on factors such as ensuring adherence to the protocol and using quality control measures to establish and maintain high standards for data quality.

The Chief Investigator (CI) and CTU will provide training to site staff on trial processes and procedures including CRF completion and data collection

On-site monitoring visits during the trial will check the accuracy of CRF entries against source documents alongside adherence to the protocol, trial specific procedures and Good Clinical Practice (GCP).

Within the CTU the clinical data management process is governed by Standard Operating Procedures which help ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH-GCP) guidelines and regulatory requirements.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify data that may be out of range, inconsistent or protocol deviations based on data validation checks programmed into the clinical trial database.

Changes to data will be recorded and fully auditable. Data errors will be documented and corrective actions implemented.

A DMEC will be convened for the study to carry out reviews of the study data at intervals during the study.

12.2 Data Collection

All data collected during study visits (including lung function data) and calls with the patient will be recorded in the source documents/electronic CRF for the study by the PI or designee. Patient identification on the CRF will be through their unique participant study number, allocated at the time of recruitment. Data will be collected and recorded on the electronic CRF by the PI or designee as per the CRF entry timelines.

In addition, the eTrack will record nebuliser usage data. When patients bring their nebuliser to the research site, this data will be transferred to a central ‘hub’ at each site via Bluetooth, from where encrypted data will be transmitted to a secure cloud platform called PARITrack. The data will be pseudoanonymised using the nebuliser device serial number as a unique trial identifier and will not contain any patient identifiable information.

Lung function data will also be collected on the mySpiroSense when patients complete spirometry at home. When patients bring their spirometer to the research site the readings will be downloaded by site staff to a local computers/laptops with software for the SpiroSense system installed. The data downloaded by the site staff can be viewed locally. At different time points the local site staff will be asked to send pseudoanonymised spirometry data to PARI using a secure method. PARI will then provide the data to the CI and researchers at Queens University Belfast in excel or other format. In addition, at the end of the study the pseudoanonymised data saved on the laptops will be available to PARI.

12.3 Data Management

Trial data including worksheet and questionnaire data will be entered onto the electronic CRF on a Clinical Trial Database (MACRO) by delegated site personnel and processed electronically as per CTU Standard Operating Procedures (SOPs) and the study specific Data Management Plan (DMP).

Data queries will be 'raised' electronically (MACRO) where clarification from site staff is required for data validations or missing data. Site staff will 'respond' electronically to data queries ensuring that amendments where applicable are made to the Clinical Trial Database.

The nebuliser usage data will be held in a secure cloud platform. The data can be accessed and viewed by authorised research personnel at each site for their patients and by the CTU and/or CI for all patients through a web based portal. Data for all patients will be provided to the CTU at the end of the treatment period in an agreed format for analysis.

When data is downloaded from SpiroSensePro spirometers and individual mySpiroSense (used by the patients at home) it can be viewed by the local research team on computers with the SpiroSense software installed. Research staff will record the required details from lung function readings taken during study visits directly into the source documents/electronic CRF for each patient. However, the data for the lung function readings completed by patients at home will be saved on computers/laptops at the site. At different time points the local site staff will be asked to send psuedoanonymised spirometry data to PARI using a secure method. PARI will then provide the data in excel or in another format to the CTU and/or Queens University Belfast research teams for analysis. In addition, at the end of the study the pseudoanonymised data saved on the laptops will be available to PARI.

All essential documentation and trial records will be stored securely and access will be restricted to authorised personnel.

All study documentation (including patient medical records) and data will be archived as per regulatory requirements and those responsible for archiving will be noted on the sponsor delegation framework/mCTA.

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size

The required sample size is 288 patients. Based on the primary outcome of mean exacerbations during 52 weeks, mean exacerbations in the control group of 0.7 and a pooled SD of 0.9 exacerbations (RESPIRE2 - 20) 162 patients would be able to detect a mean difference between groups of 0.4 exacerbations with 80% power and at the 5% significance level. To allow for a potential interaction between the two interventions, 50% inflation has been included, to 243 patients. Assuming approximately 15% dropout gives a total of 288 patients (72 in each of the four groups).

The actual mean difference observed in the RESPIRE2 trial was 0.3 exacerbations for the 28 Day Cycle. The mean exacerbation rate observed in the RESPIRE2 placebo group was 0.7 exacerbations over 48 weeks which is lower than reported in other studies (BAT Trial - 21, BLESS Trial - 22, EMBRACE Trial - 23). It is postulated that new larger clinical trials may be reporting a lower rate of Protocol defined pulmonary exacerbation than in the previous literature potentially due to improvements in definitions of exacerbations and/or increased standardisation across centres in multi-centre studies.

This sample size would provide over 80% power to detect a minimally important difference of 8 points for the QoL-B scale (SD of 18) at the 5% significance level (8, 18). This sample size would also be sufficient to detect a 75% increase in median time to exacerbation at 94% power and a medium effect size for the other secondary outcomes at 88% power and 5% level of significance'

13.2 Statistical methods

Standard approaches will be used to detect patterns in missing data. Baseline characteristics, follow-up measurements (including week 104) and safety data will be described using the appropriate descriptive summary measures depending on the scale of measurement.

The primary analysis will be conducted on a modified intention to treat basis. The modified intention-to-treat population will consist of randomised participants that have data from at least one post baseline efficacy assessment. A per-protocol analysis may also be conducted which will involve a comparison of treatment groups that includes only those participants who completed the treatment originally allocated and did not have protocol deviations.

Groups will be compared for the primary outcome (number of exacerbations over the 52 weeks) and antibiotic use (number of days of antibiotic use over the 52 weeks) using Negative Binomial regression. The regression models will be used to adjust for baseline characteristics and other covariates. Groups will be compared for QoL-B and other continuous outcomes using analysis of covariance (ANCOVA). ANCOVA will be used to adjust for baseline characteristics and other covariates.

The factorial design permits the separate testing of the effects of HTS and carbocisteine on HRQoL and the detection of any interaction between them. These tests will be implemented using three contrasts (representing HTS, carbocisteine, and the interaction) in the models.
For time to next exacerbation, Kaplan-Meier curves will be prepared and the log-rank test calculated to compare the groups.

Analyses will be two-sided and tested at an a priori significance level of p=0.05. The primary time point has been defined as the 52-week time point. There is no adjustment for multiple testing at the different time points, as the primary outcome has been defined and prioritised.

Further details and description will be given in the Statistical Analysis Plan.

13.3 Health economics evaluation

A within trial economic evaluation will assess the cost-effectiveness of the four treatment options at 26 and 52 week time points. Following NICE guidance on methods for technology appraisal (24), the perspective of the analysis will be the NHS and Personal Social Services. A within-the-table analysis will be performed, treating the four options in the factorial design as mutually exclusive treatments. Economic outcomes will then be estimated and presented separately for each treatment option so that the effect of any interactions can be seen directly. An incremental analysis will allow us to identify the treatment that offers the best value for money relative to the standard care option and further incremental analysis will be undertaken to estimate whether any other strategies are dominated. We will estimate the cost per QALY gained, the cost per exacerbations avoided and the net benefit (NB) for each of the treatment arms. Regression analysis with an interaction term will also be performed, as a robustness check and also as this will allow us to control for baseline covariates. The choice of the incremental cost-effectiveness estimate will be determined by the significance of the interactions and the sensitivity of results to estimates where interactions are allowed and where they are excluded.

Participants' health service use (both related and unrelated to their BE) will be collected from baseline to 52 weeks. At baseline participants will be asked about their service use in the previous four weeks so that baseline costs can be adjusted for in the analysis. Participants will be given Health Service Use Logs at baseline, 2, 8 and 26 weeks to record their use of services prospectively. At 2, 8, 26 and 52 weeks they will be asked to use the log to complete the Health Service Use Questionnaire which will include questions on additional routine/long-term prescription use and prescriptions relating to specific GP and hospital visits. Costs will be calculated by attaching appropriate unit costs from national sources.

Generic HRQoL will be measured using the EQ-5D-5L at baseline, 2 weeks, 8 weeks, 26 weeks and 52 weeks. The resulting utilities will be used to calculate QALYs.

Uncertainty surrounding these incremental cost-effectiveness ratios will be summarised in cost effectiveness acceptability curves showing the probability of the therapeutic strategies being cost-effective at different threshold levels of willingness-to-pay per QALY and per exacerbation avoided. Sensitivity analysis will be performed to explore the impact on cost effectiveness of variations in key parameters. Further details will be provided in a health economic analysis plan.

13.4 Additional analyses

A secondary analysis will be conducted which will focus on exploring the effect of adherence on the trial's primary and secondary outcomes. There is emerging agreement that for a treatment to be effective an adherence level of greater or equal to 80% is required. Therefore, following completion of the main study analysis, a secondary analysis of the adherence data to categorise patients as adherent or non-adherent. This adherence data will allow us to explore if there is a close response relationship between dose and quality of life. The data will then be explored to ascertain whether there are any predictors of adherence.

13.5 Definition of Pulmonary Exacerbations

A summary of the EMBARC definition of pulmonary exacerbations is included in table 2, and a comprehensive definition is detailed in Appendix 1.

Table 1: Summary of EMBARC definition of pulmonary exacerbations

Criteria for the EMBARC definition	
The EMBARC definition consists of three parts that must all be satisfied for a fully qualifying exacerbation. If part 3 is met with either part 1 or part 2 it is defined as a partially qualifying exacerbation (PQE).	
Part 1- Symptoms	Patient must present with deterioration in 3 or more of the 6 following symptoms: 1. Cough 2. Sputum volume/consistency 3. Sputum purulence 4. Breathlessness/exercise tolerance 5. Fatigue and or Malaise 6. Haemoptysis
Part 2- Time	Symptoms must be present for at least 48 hours.
Part 3- Treatment	A change in bronchiectasis treatment not limited to antibiotics.
For separate exacerbations there must be an unequivocal resolution of symptoms from the first event and >14 days to the commencement of a subsequent event. If this criterion is not met then the exacerbation is counted as a single continuous event.	

14 PHARMACOVIGILANCE

Timely, accurate and complete reporting and analysis of safety information from clinical trials is crucial for the protection of patients and is mandated by regulatory agencies.

14.1 Definition of Adverse Events

The European Clinical Trials Directive 2001/20/EC and applicable clinical trial regulations set out the legal requirements for AE recording, management and reporting of clinical trials.

Table 2: Terms and Definitions for AEs

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product, **which is related** to any dose, administered to that subject.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which **is not consistent** with the Reference Safety Information (RSI) about the medicinal product in question:
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any adverse event or adverse reaction that: • Results in death: Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring within 30 days of the last administration of the study agent must be treated as a SAE and reported as such. All deaths, which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAR and reported as such. • Is life-threatening: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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. • Requires hospitalisation or prolongation of existing hospitalisation: hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Therefore, patients do not need to be hospitalised overnight to meet the hospitalisation criteria. Hospitalisation (including for an elective procedure) for a pre-existing condition (prior to study entry) which has not worsened does not constitute a serious experience. • Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions) • Consists of a congenital anomaly or birth defect (in offspring of subjects or their partners) taking the IMP regardless of time of diagnosis 'Important medical events' may also be considered serious if they jeopardise the subject or required an intervention to prevent one of the above consequences. They also include • Overdoses (accidental or intentional) • Pregnancy outcome (of subject or partner) • An alarming adverse experience • Non-serious AEs and/or laboratory abnormalities, which are listed in the trial, protocol as critical to safety evaluations and requiring reporting.

Suspected Serious Adverse Reaction (SSAR)	Any adverse reaction that is classed in nature as serious and **is consistent** with the Reference Safety Information (RSI) about the medicinal product in question:
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any adverse reaction that is classed in nature as serious and **is not consistent** with the Reference Safety Information (RSI) about the medicinal product in question:

*Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

14.2 AE Reporting

The PI or designee will record all directly observed AEs and all AEs spontaneously reported by the patient. In addition, the patient will be asked about AEs at each visit following initiation of treatment. Signs and symptoms of pulmonary exacerbations collected as outcomes of the trial will not be reported as AEs. However if a patient experiences an exacerbation between the period of consent and randomisation this should be recorded and reported as an adverse event. All AEs should be recorded in the patient's notes and reported on the AE form within the CRF. The PI or designee must assess all AEs for seriousness, causality, severity. For any AEs assessed as possibly, probably or definitely related to the study drug the PI or designee must also assess expectedness.

14.3 Assessment of Seriousness

The PI or designee should make an assessment of seriousness i.e. is this is an AE, AR or suspected unexpected adverse reaction that:

- Resulted in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation*
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

* Signs and symptoms of pulmonary exacerbations collected as outcomes of the trial 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.

14.4 Assessment of Causality

The PI or designee should make an assessment of causality, i.e. the extent to which it is believed that the event may be related to the study drug:

- **Not Related:** Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.

- **Unlikely:** Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
- **Possibly*:** Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.
- **Probably*:** Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the product than any other cause.
- **Definitely*:** Temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

* Where an event is assessed as possibly, probably or definitely related, the event is an AR.

14.5 Assessment of Severity

The PI or designee should make an assessment of severity for each AE according to the following categories:

- **Mild (Grade 1):** A reaction that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate (Grade 2):** A reaction that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe (Grade 3):** A reaction that prevents normal everyday activities.
- **Life Threatening (Grade 4):** A reaction that has life threatening consequences; urgent intervention indicated.
- **Death (Grade 5):** A reaction that results in death.

14.6 Assessment of Expectedness

The Sponsor is required to make an assessment of expectedness and this is delegated to the PI. The PI or designee is required to make an assessment of expectedness of ARs based on the reference safety information (RSI) as documented in relevant product information such as the summary of product characteristics (SPC) and ARs may be classed as either:

- **Expected:** The AR is consistent with the toxicity of the study drug listed in the SPC.
- **Unexpected:** The AR is not consistent with the toxicity in the SPC.

The reference safety information for this study is the version of the SPC for carbocisteine (Mucodyne®) (section 4.8 undesirable effects) and Patient Leaflet for Mucoclear® (Side effects section) as approved by the Medicines and Healthcare Products regulatory Agency.

An AR may be described as ‘unexpected’ if it has occurred with greater frequency or severity that might otherwise have been expected.

14.7 Serious Adverse Event Reporting

A SAE is defined as an AE that fulfils one or more of the criteria for seriousness outlined in Table 4. SAEs will be evaluated by the PI or designated investigator for causality (i.e. their relationship to the study drug) and expectedness (if related). SUSARs are SAEs that are considered to be caused by the study drug and are unexpected i.e. their nature or severity is not consistent with the RSI.

SAEs will be reported using the SAE form and must be reported to CTU within 24 hours of becoming aware of the event. The form must be emailed to CTU using the following dedicated email address:

clinicaltrials@nictu.hscni.net

The site should not wait until all information about the event is available before notifying the CTU of the SAE. The CTU will acknowledge receipt of the SAE Form within two working days by email to the site. Information not available at the time of the initial report must be documented on a follow up SAE Form. Follow up information should be sought and submitted as it becomes available.

The CTU is responsible for reporting SAEs to the Sponsor, ethics committee, and MHRA within the required timelines as per the regulatory requirements. A fatal or life threatening SUSAR must be reported within 7 days after the CTU has first knowledge of such an event. Relevant follow up information will be sought and communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and research ethics committees within 15 days after the knowledge of such an event.

14.8 Adverse Event Reporting Period

The AE reporting period for the trial begins upon enrolment into the trial and ends 30 days following the last administration of the study drug. All AEs assessed by the PI as possibly, probably or definitely related to the study drug and all SAEs that occur during this time will be followed until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

14.9 Recording and Reporting of Urgent Safety Measures

If the PI or designee becomes aware of information that necessitates an immediate change in study procedure to protect clinical trial participants from any immediate hazard, they can implement this immediately prior to approval by REC/MHRA.

They should phone the clinical trials unit at the MHRA and discuss the issue with a medical assessor once an urgent safety measure was taken. They should also report the urgent safety measure within 1 working day to the CTU who will notify the Sponsor.

The PI or designee should respond to queries from the Sponsor immediately to ensure the adherence to reporting requirements to REC and Competent Authority (CA).

14.10 Pregnancy Reporting

Pregnancy is not considered an AE or SAE however an abnormal outcome would be. Therefore, the PI or designee must collect pregnancy information for female participants, and for females who become pregnant while their partners are participating in the trial. Consent should be obtained to follow up the pregnancy from the female partners of male participants.

The pregnancy reporting period for the trial is from the commencement of the study drug until 30 days post admin of the final dose of study drug. The PI or designee should complete and submit the Pregnancy Reporting Form to the CTU by email within 14 days of being made aware of the pregnancy. The CTU will acknowledge receipt of the Pregnancy Reporting Form within two working days by email to the site.

Any pregnancy that occurs in a participant or participant's partner during the trial should be followed to outcome. Follow up/outcome information should be provided to the CTU as soon as it becomes available.

14.11 Eflow, Etrack, SpiroSensePro and MySpiroSense Product Complaint Reporting

Throughout the course of the CLEAR trial, if site staff become aware, either through use or as reported by patients, of any issues with the eFlow, eTrack, SpiroSensePro or MySpirosense equipment, these should be reported in accordance with the Study Specific Guideline.

15 DATA MONITORING

15.1 Access to Trial Data

Prior to commencement of the study, the PI at each site will give permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Consent from patients for direct access to data will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.2 Monitoring arrangements

The CTU will be responsible for trial monitoring. Monitoring will be conducted in accordance with the trial monitoring plan. Monitoring will be an on-going activity from the time of initiation until trial close-out and will comply with the principles of Good Clinical Practice (GCP) and European Union (EU) directive 2001/20/EC. The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor.

Before the trial starts at a participating site, trial initiation checks and training will take place to ensure that all relevant essential documents and trial supplies are in place and that site staff are fully aware of the trial protocol and procedures. Monitoring during the trial will check the accuracy of entries on CRF's against the source documents, the adherence to the protocol, procedures and GCP, and the progress of patient recruitment and follow up.

The PI or designee should ensure that access to all trial related documents including source documents (to confirm their consistency with CRF entries) are available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan.

The close out procedure at each site will commence once the final patient enrolled has completed all follow-up required by the protocol.

16 TRIAL COMMITTEES

16.1 Trial Management Arrangements

The CI will have overall responsibility for the conduct of the study. The CTU will undertake trial management including preparing clinical trial applications (MHRA, REC and research governance), pharmacovigilance, site initiation/training, monitoring, analysis and reporting. The Trial Manager/Co-ordinator will be responsible on a day-to-day basis for overseeing and co-ordinating the work of the multi-disciplinary trial team. Additional trial specific oversight committees will be convened for the CLEAR trial. These will include a Trial Management Group (TMG), Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC). The CTU will facilitate in the setting-up and the co-ordination of these trial committees.

16.2 Trial Management Group (TMG)

A TMG will be established. The TMG will have representation from the CTU and other investigators/collaborators who are involved in the study and provide trial specific expertise (e.g. trial statistician). This group will have responsibility for the day to day operational management of the trial, and regular meetings of the TMG will be held to discuss and monitor progress. The discussions of the TMG will be formally minuted and a record kept in the TMF.

A TMG Charter will be drawn up to detail the terms of reference of the TMG including roles and responsibilities.

16.3 Trial Steering Committee (TSC)

A group of experienced clinicians, trialists and lay people will act as a TSC. The TSC will provide oversight with respect to the conduct of the study on behalf of the Funder and Sponsor.

The TSC will have at least 75% independent member ship. It will include the CI, independent clinicians (1 of whom will act as chair) and lay representatives. The TSC will meet during the course of the trial and observers may be invited and be in attendance at TSC meetings, such as the Sponsor or Funder representatives or the Trial Manager to provide input on behalf of the CTU.

A TSC charter will be drawn up to detail the terms of reference of the TSC including membership and roles/responsibilities.

16.4 Data Monitoring and Ethics Committee (DMEC)

The role of the DMEC is to safeguard the rights, safety and wellbeing of trial participants, monitor data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue and monitor the overall conduct of the study to ensure the validity and integrity of the study findings. The DMEC will meet annually.

The DMEC will comprise independent members with at least one statistician and two respiratory specialists.

A DMEC charter will be drawn up to detail the terms of reference of the DMEC including membership and roles/responsibilities.

17 REGULATIONS, ETHICS AND GOVERNANCE

The trial will comply with the principles of GCP, the requirements and standards set out by the EU Directive 2001/20/EC and the applicable regulatory requirements in the UK, the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Research Governance Framework.

17.1 Sponsorship

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor, CI and each organisation who will undertake Sponsor delegation duties in relation to the management of the study.

17.2 Funding

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA). This funding covers staff cost, travel, consumables, training, trial registration fees, software licenses and open access publication fees.

This study is funded as a result of a commissioned call from the NIHR and the protocol was developed in response to review by NIHR HTA.

PARI GmbH will also provide non-financial support to this study through the provision of HTS 6%, eFlow's, spirometers and associated technology for processing and accessing collected data.

17.3 Contributorship

Judy Bradley, Brenda O'Neill, Stuart Elborn, Danny McAuley and Michael Clarke initiated the study design. All the applicants (Judy Bradley, Brenda O'Neill, Stuart Elborn, Danny McAuley Michael Clarke, James Chalmers, Michael Loebinger, Adam Hill, Jamie Duckers, Fiona Copeland, Mary Carroll, Anthony De-Soyza, Evie Gardner and Ashley Agus), alongside the TMG were involved in the development and finalisation of the protocol. Fiona Copeland provided expertise on patient and public involvement. Michael Clarke provided expertise in trial methodology. Evie Gardner and Mairead North provided statistical expertise in trial clinical trial design. Ashley Agus and Alistair McGuire provided health economics expertise. A statistician from the NICTU will conduct the statistical analysis and Ashley Agus will conduct the health economics analysis.

17.4 Patient and Public Involvement

Service users have been involved in this proposal in both a consultative and collaborative capacity. They have influenced the choice of interventions and the outcomes to measure. Participants in our proof of concept study gave their views on the role of mucoactives in bronchiectasis (BE) and these views informed this proposal. Fiona Copeland, Chair of Primary Ciliary Dyskinesia Family Support Group UK and a BE carer is a co-applicant, helped develop the proposal, and (pending HTA approval) has agreed to be a member of the TSC.

The study will be registered with the INVOLVE open-access database which registers research health care projects involving members of the public as partners in the research process.

17.5 Competing Interests

The research costs were funded by NIHR HTA. The CI and members of the TMG have no financial or non-financial competing interests and the members of the DMEC/TSC will be asked to confirm that they have no conflict of interest. In the event that a DMEC/TSC member reports a conflict of interest, advice will be sought from the sponsor.

17.6 Indemnity

Queen's University Belfast will provide indemnity for the design of the protocol and the BHSCT will provide indemnity for the management of the CLEAR study. The NHS indemnity scheme will apply with respect to clinical conduct and clinical negligence.

17.7 Regulatory and Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee.

Appropriate REC and MHRA approvals will be obtained for the study.

17.8 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). All members of the trial team will be required to have GCP training.

17.9 Protocol Compliance

A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented on the protocol deviation form.

A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

i. the safety or physical or mental integrity of the subjects of the trial; or
ii. the scientific value of the trial

The PI or designee is responsible for ensuring that serious breaches are reported directly to the CTU within one working day of becoming aware of the breach. The CTU will notify the CI and sponsor.

17.10 Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee and the Regulatory Authority. Changes to the protocol may require regulatory authority/ethics committee approval/favourable opinion prior to implementation, except when modification is needed to eliminate an immediate hazard(s) to patients. The CTU in collaboration with the sponsor will submit all protocol modifications to the competent authority/research ethics committees for review in accordance with the governing regulations.

17.11 Patient Confidentiality

In order to maintain confidentiality, all CRF's, questionnaires, study reports and communication regarding the study will identify the patients by the assigned unique trial identifier and initials only. Databases where information will be stored will be password protected. Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

17.12 Record Retention

The PI will be provided with an Investigator Site File (ISF) by the CTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The Trial Master File (TMF) will be held by the CTU within the BHSCT and the essential documents that make up the TMF will be listed in an SOP. On completion of the trial, the TMF and study data will be archived by the CTU according to the applicable regulatory requirements and for up to 15 years as required by the BHSCT Sponsor. The PI is responsible for archiving of essential documents at local sites in accordance with the requirements of the Sponsor and local policies. The PI has a responsibility to allow Sponsor access to archived data and can be audited by the Sponsor or competent authority on request. Following confirmation from the Sponsor the CTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the CTU and Sponsor.

18 DISSEMINATION/PUBLICATIONS

18.1 Trial Registration

The trial will be registered with the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database and the International Standard Randomised Controlled Trial Number (ISRCTN) register. We also plan to register the protocol of our trial on clinical trials.gov, providing details of our methodology and statistical analysis plan to ensure transparency.

18.2 Trial Publications

The final study report will be provided by the Trial Statistician; it is anticipated that the study findings will be presented at national and international meetings with abstracts on-line. Presentation at these meetings will ensure that the results and its implications quickly reach clinical staff involved in the management of patients with BE. In accordance with the open access policies proposed by the NIHR we aim to publish:

i. the trial protocol;
ii. the clinical findings of the trial and;
iii. a paper describing the cost-effectiveness in the NHS setting in high quality peer-reviewed open access (via PubMed Central) journals.

The findings of this study will be disseminated to specific groups and may in the future help inform guidelines created by the following:

- British Thoracic Society
- National BE Guideline Group
- European guidelines
- Physiotherapy guidelines and undergraduate and postgraduate physiotherapy teaching
- NHS managers and commissioners
- NIHR HTA journal
- Publications will be made readily accessible to the public, health care professionals and commissioners

In addition, a lay person's summary will be sent to local and national patient support and liaison groups including the European Lung Foundation BE Patient Advisory Group and the British Lung Foundation (UK), as well as similar organisations in devolved nations. A report of the study findings will be sent to the INVOLVE registry. This is an open-access database which registers research health care projects involving members of the public as partners in the research process. Following peer reviewed publication, appropriate key findings will also be posted on institutional websites available to the general public. In addition, the most significant results will be communicated through press releases to ensure dissemination to the broader public and research participants.

18.3 Authorship Policy

An author will be considered to be someone who has made a substantive intellectual contribution to the study. All investigators, Trial Statistician and relevant members of the Trial Management Group will potentially be co-authors. Collaborators will be acknowledged.

Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org).

18.4 Data Sharing Statement

Requests for data sharing will be reviewed on an individual basis by the CI and TMG.

18.5 Data Access

Following the publication of the primary, secondary and tertiary study outcomes, there may be scope to conduct additional analyses on the data collected. In such instances formal requests for data will need to be made in writing to the CI who will discuss this with the TMG. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission. Authorship will need to take the format of "[name] on behalf of the CLEAR Clinical Trial Group" or something similar which will be agreed by the TMG.

19 REFERENCES

1. British Thoracic Society BE(non-CF) Guideline group. Guideline for non-CF BE. Thorax 2010; 65: Supplement 1.
2. Chalmers, J, Elborn J, Editorial Reclaiming the name bronchiectasis – BMJ Thorax 2015; 70:399-400.
3. Nicotramb Rivera Dale AM Clinical, pathophysiological and microbiological characterisation of bronchiectasis in an aging cohort, Chest 1995; 108:955-61
4. Wilson CB Bore PW O Leary CT Validation of the St George's Respiratory Questionnaire in Bronchiectasis AM J Critical Care Medicine 1997; 156:536-41.
5. Smith A Non CF Bronchiectasis J R Coll Physicians Edinburgh 2011; 41:132.
6. McCullough AR, Tunney MM, Elborn, SJ, Bradley JM, Hughes CM. Predictors of adherence to treatment in bronchiectasis. Respiratory Medicine 2015; 109(7): 838-845.
7. Hill AT, Rowth C, Welhams. National BTS Bronchiectasis audit 2012: Is the quality standard being adhered to an adult in secondary care. Thorax-jnl-2013-203739.
8. Bradley JM, Treacy K, O'Neill B, McCourt F, Green L, Gardner E, Elborn JS. A Randomised double blind 13-week crossover trial of hypertonic saline (HTS) (6%) vs isotonic saline (ITS) (0.9%) in patients with BE. Thorax 2011; 66: A49.
9. Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in BE. Respiratory Medicine 2011; 105(12):1831-35.
10. Kellett F, Redfern J, Niven RM. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable BE. Respiratory Medicine 2005; 99 (27): e31.
11. Nicolson CHH, Stirling RG, Borg BM, Button BM, Wilson JW, Holland AE. The long-term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respiratory Medicine 2012; 106, 661e667.
12. Poole P, Chong J, Cates CJ. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD001287. DOI: 10.1002/14651858.CD001287.pub5.
13. Nolan SJ, Thornton J, Murray CS, Dwyer T. Inhaled mannitol for cystic fibrosis. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD008649. doi: 10.1002/14651858.CD008649.pub2.
14. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Annals of Internal Medicine 2010;152. Epub 24 March.
15. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, Altman DG, Barbour V, Macdonald H, Johnston M, Lamb SE, Dixon-Woods M, McCulloch P, Wyatt JC, Chan AW, Michie S. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. British Medical Journal. 2014 Mar 7;348:g1687. doi: 10. 1136/bmj. g1687.
16. Rowan S, Elborn JS, Ennis M, Bradley JM. Clinimetric properties of outcome measures in BE. European Respiratory Journal 2012; A2278.
17. Spinou A, Fragkos KC, Lee KK, Elston C, Siegert RJ, Loebinger, MR, Wilson R, Garrod R, Birring SS.The validity of health-related quality of life questionnaires in bronchiectasis: a systematic review and meta-analysis. Thorax doi:10.1136/thoraxjnl-2015-207315.
18. Quittner AL, O'Donnell AE, Salathe MA, Lewis SA, Li X, Montgomery AB, O'Riordan TG, Barker AF Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. Thorax. 2015 Jan; 70(1):12-20.
19. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life

research: an international journal of quality of life aspects of treatment, care and rehabilitation 2011; 20(10):1727-36.
20. RESPIRE2 – personal communication pre-publication.
21. Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, Koppers RJ, van der Werf TS, Boersma WG. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. Journal American Medical Association. 2013 Mar 27;309(12):1251-9.
22. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, Biga S, Schlebusch S, Dash P, Bowler SD. Effect of Long-term, Low-Dose Erythromycin on Pulmonary Exacerbations Among Patients with Non–Cystic Fibrosis Bronchiectasis. The BLESS Randomized Controlled Trial Journal American Medical Association. 2013; 309 (12):1260-1267. doi:10.1001/jama.2013.2290.
23. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, Milne D, Fergusson W, Tuffery C, Sexton P, Storey L, Ashton T. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet. 2012 Aug 18;380(9842):660-7.
24. NICE. 2013 [cited March 7 2016]. Available from: http://publications.nice.org.uk/guideto-th-methodsof-technologyappraisal-2013-pmg9.
25. Pulmonary Exacerbation in Adults with Bronchiectasis: A Consensus Definition for clinical research. Adam T Hill,1 Charles S Haworth*,2 Stefano Aliberti,3 Alan Barker,4 Francesco Blasi,3 Wim Boersma,5 James D Chalmers,6 Anthony De Soyza,7 Katerina Dimakou,8 J Stuart Elborn,9 Charles Feldman,10 Patrick Flume,11 Pieter C Goeminne,12,13 Michael R Loebinger,14 Rosario Menendez,15 Lucy Morgan,16 Marlene Murris,17 Eva Polverino,18 Alexandra Quittner,19 Felix C Ringshausen,20 Gregory Tino,21 Antoni Torres,22 Montserrat Vendrell,23 Tobias Welte,24 Rob Wilson,25 Conroy Wong,26 Anne O' Donnell**,27 Timothy Aksamit.28 The EMBARC/BRR definitions working group. European Respiratory Journal 2017 (In Press)

20 APPENDICES

20.1 Table of Appendices

Appendix 1	Definition of Exacerbation
Appendix 2	Validity and sensitivity of the EMBARC definition for exacerbations in bronchiectasis: A sub-study within the CLEAR trial
Appendix 3	Spirometry Substudy
Appendix 4	Optimising Recruitment and Retention: Implementing Studies Within A Trial (SWATs) with the CLEAR clinical trial
Appendix 5	Is the mechanism of action of hypertonic saline and/or carbocisteine in the treatment of patients with bronchiectasis due to a decrease in sputum viscoelasticity, inflammation and bacterial load?

20.2 Appendix I: Definition of Exacerbation

- The exacerbation definition is in three parts; Part 1 - Symptoms; Part 2 – Duration of Symptoms; Part 3 – Decision to Treat. Part 1: Symptoms of a bronchiectasis exacerbation requires at least three of the following: increased cough; increased sputum volume or change in sputum consistency; increased sputum purulence; increased breathlessness and/or; decrease exercise tolerance; fatigue and/or malaise; haemoptysis. Part 2: Duration of Symptoms requires symptoms to be present for 48 hours or more. Part 3: Physician decision to treat requires that the physician determines that change in bronchiectasis treatment is required. For CLEAR, this change of treatment will be defined as the prescription of antibiotics. As this definition will likely be used as the standard definition in all future bronchiectasis trials we propose to use it within our bronchiectasis trial.

- To classify as a fully qualifying exacerbation in the proposed study the exacerbation will have to meet the requirements of all three parts of the definition.

- In some instances, patients or physicians diagnose and treat exacerbation symptoms with antibiotics which do not meet these criteria. In the proposed study we will define these as partially qualifying exacerbations. A partially qualifying exacerbation is one that meets part 3 (i.e. prescription of antibiotics) and either part 1 or part 2 of the EMBARC definition. If only part 3 is met then an other form of exacerbation occurred. The study will adopt an adjudication method where an independent panel throughout the study will adjudicate exacerbations in terms of categorising them as a fully qualifying exacerbation, partially qualifying exacerbation, other exacerbation or no exacerbation

- The study will adopt the methodology used in the BLESS randomised controlled trial which will improve the validity of diagnosed exacerbations and ensure differentiation of sequential exacerbations (22, 25). For example, in order to be counted as separate exacerbations, sequential episodes will require unequivocal resolution of symptoms from the first event AND >14 days from the end of one event to the commencement of the subsequent event. If both criteria were not met, the exacerbation was counted as a single, continuing event.

- In order to ensure that both first and sequential exacerbations are captured all patients in the study will be provided with contact details of study staff to use should they develop either symptoms of exacerbation or feel that they required antibiotic therapy. Many patients hold prophylactic antibiotics at home but will be directed and regularly reminded at each study visit to contact study staff when feeling unwell. This will ensure that prescription of their prophylactic or other antibiotics is directed through clinical staff.

- To minimise patient burden / investigators at each site will were possible assess via telephone call if patients meet criteria for an exacerbation and if this is the case will arrange for a prescription be made available either at the subject's local pharmacy or for collection at the study centre. If symptoms are inconsistent with an exacerbation, and/or the subject was too unwell to complete assessments via telephone then patients may be invited to make an unscheduled study visit.

- At potential exacerbations i.e. during each phone call to diagnose potential exacerbations the RSSQ will be used to collect symptoms linked to exacerbation either by telephone call or unscheduled visit (when required). In the questionnaire, we will

need to change “since last visit” to “48 hours or more”. In addition, the questionnaire will be used to collect symptoms at the resolution of an exacerbation. In the questionnaire we will need to change “since last visit” to “since the start of their antibiotics". Modified versions of the RSSQ questionnaire will be used as an outcome at each study visit to look at symptoms and when patient has a potential exacerbation.

- The SpiroSense lung function machine has a patient mobile attachment (mySpiroSense) which facilitates monitoring of lung function at home, in addition to the PC spirometer. During the main trial, it will allow assessment of lung function (in the patient’s home) alongside assessment of symptoms when the patients are feeling unwell and when a decision regarding diagnosis of an exacerbation (important secondary outcome) has to be made.

- Additionally, all measurements collected at commencement of an exacerbation will also be collected at resolution of exacerbation (end of antibiotic course + 2 weeks) by a follow-up telephone call.

20.3 Appendix II: Validity and sensitivity of the EMBARC definition for exacerbations in bronchiectasis: A sub-study within the CLEAR trial

Authors:	Rohan Anand, Professor Judy Bradley, Professor Mike Clarke, Professor Danny McAuley, Dr Brenda O'Neill, Professor Stuart Elborn
Study Details	
CLEAR Study Title:	A 2x2 factorial randomised open label trial to determine the clinical and cost- effectiveness of hypertonic saline (HTS 6%) and carbocisteine for airway clearance versus usual care over 52 weeks in bronchiectasis
Sub-study Title:	Validity and sensitivity of the EMBARC definition for exacerbations in bronchiectasis

Table of Contents

20.3.1 List of Abbreviations:

ANOVA	Analysis of Variance
BE	Bronchiectasis
CLEAR	A 2x2 factorial randomised open label trial to determine the clinical and cost- effectiveness of hypertonic saline (HTS 6%) and carbocisteine for airway clearance versus usual care over 52 weeks in bronchiectasis
CRF	Case Report Form
CT	Computed Tomography
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
eCRF	electronic Case Report Form
EMBARC	European Multicentre Bronchiectasis Audit and Research Collaboration
FEV_1	Forced Expiratory Volume in 1 second
FQE	Fully Qualifying Exacerbation
FVC	Forced Vital Capacity
HRCT	High-Resolution Computed Tomography
HTS	Hypertonic Saline
NICTU	Northern Ireland Clinical Trials Unit
PI	Principal Investigator
PQE	Partially Qualifying Exacerbation
RSSQ	Respiratory and Systemic Symptoms Questionnaire

20.3.2 Introduction:

20.3.2.1 Background:

Bronchiectasis is a permanent widening of the bronchi and bronchioles due to destruction of elastic muscle tissue that can lead to a loss of function in mucociliary clearance mechanisms. The resulting uncleared secretions can accumulate, providing a favourable environment for microbial infections within the pulmonary airways (Rademacher, Welte 2011). In addition to infection, a sustained and increased inflammatory response leads to further destruction of the airway wall and muscle, dilation of the airways and an accumulation of sputum. This destructive cycle can continue in bronchiectasis patients, resulting in worsening of their condition. In addition, colonisation and infections can cause bronchiectasis related pulmonary exacerbations, as can some non-microbial factors such as pollution and viruses (Redondo, Ferri et al. 2016) These exacerbations represent a major decline of a person's normal pulmonary health and functioning compared to an individual's day to day variation. To the patient these exacerbations can be debilitating especially if symptoms result in hospitalisation. Such exacerbations usually require the administration of antibiotics for a successful resolution.

There is ambiguity surrounding the definition of pulmonary exacerbations. The definition varies between organisations and clinicians with regards to what signs, symptoms and measurements contribute towards a diagnosis of an exacerbation. Signs are those patient phenomena that can be observed by a healthcare practitioner or provider and are usually objective and indicative of a problem (e.g. haemoptysis). Symptoms are patient-reported phenomena that are reported but not necessarily observed by anyone other than the patient and are usually subjective (e.g. fatigue). Some clinical phenomena can be both a sign and a symptom (e.g. a patient-reported cough that is also observed by their healthcare provider).

Common signs and symptoms that are used to define exacerbations include increased cough, sputum, dyspnoea, fatigue, wheezing, haemoptysis and a decline of lung function (FEV_1 and FVC). The British Thoracic Society (BTS) guidelines defines an exacerbation as the deterioration of at least three of the following respiratory symptoms: cough, increased sputum production, volume, purulence or change in viscosity with or without increasing wheeze, increased dyspnoea, haemoptysis, and chest pain for a period greater than 24 hours with or without systemic systems, such as fever and alterations in a chest radiograph (Pasteur, Bilton et al. 2010). In contrast, the American Thoracic Society (ATS) describes common exacerbation indicators as increased sputum (volume, viscosity, or purulence), increased in cough, wheezing, a shortness of breath, haemoptysis and a decline in lung function (McShane, Naureckas et al. 2013). In another contrast, the Spanish Society of Pneumology and Thoracic Surgery defines a bronchiectasis exacerbation as an increase of volume and purulence in sputum or a change in sputum (consistency, viscosity or haemoptysis) with or without systemic symptoms such as fever, cough, asthenia, anorexia, weight loss and pleural pain (Vendrell, de Gracia et al. 2008). Although these descriptions have similarities, the variability in how the signs and symptoms are used have led others to define exacerbations purely in terms of the decision to treat with antibiotics (Chang, Bilton 2008).

Bronchiectasis exacerbation definitions are modelled on Fuch's criteria, which originated in cystic fibrosis (Fuchs, Borowitz et al. 1994) and defined an exacerbation as the requirement for antibiotics following changes in four out of twelve signs or symptoms (see Appendix 1). Modifications of the Fuch's criteria are the most commonly used definition for bronchiectasis exacerbations. They have been used in subsequent prospective and retrospective bronchiectasis studies to measure exacerbations depending on what signs/symptoms the investigators think should constitute an exacerbation in the context of their research (Tsang, Tan et al. 2005, Tsang, Ho et al. 1998, Mao, Yang et al. 2016, Finklea, Khan et al. 2010). An example of such is in the landmark trial exploring the efficacy of DNase in bronchiectasis (O'Donnell, Barker et al. 1998) where investigators used the Fuch's criteria but modified it for use in non-cystic fibrosis bronchiectasis by selecting 9 key parameters to measure (see Appendix 2).

The various combinations of signs/symptoms used to measure exacerbations can lead to differences in the number and duration of exacerbations reported across trials. The lack of consensus for defining and recording exacerbations in bronchiectasis clinical research, makes

it difficult to compare, contrast and combine the findings for exacerbations across different studies, limiting the use of meta-analyses to resolve important uncertainties about treatment efficacies.
Recently a standard consensus definition has been developed for measuring pulmonary exacerbations specific for bronchiectasis. In 2016, bronchiectasis experts from across the world met at the first World Bronchiectasis Conference in Germany (Hill 2017) with an aim of developing a consensus definition for an exacerbation that could be used in future clinical trials. A Delphi process and roundtable meeting were used to formulate a definition named the EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration) definition. This definition will be explored and compared for the first time against a conventional modified Fuch's criteria to measure for pulmonary exacerbations in the CLEAR trial, a novel bronchiectasis trial that will take place in the United Kingdom from 2017, and the methods to be compared are described below.
The criteria for the EMBARC definition are summarised in the table below:

Table 2: Summary of the three parts of the EMBARC definition for bronchiectasis exacerbations

Criteria for the EMBARC definition	
The EMBARC definition consists of three parts which must all be satisfied for a fully qualifying exacerbation. If part 3 is met with either part 1 or part 2 it is defined as a partially qualifying exacerbation (PQE).	
Part 1- Symptoms	Patient must present with deterioration in 3 or more of the 6 following symptoms: 1. Cough 2. Sputum volume *and/or* Consistency 3. Sputum purulence 4. Breathlessness *and/or* Exercise tolerance 5. Fatigue *and/or* Malaise 6. Haemoptysis
Part 2- Time	Symptoms must be present for at least 48 hours.
Part 3- Treatment	A change in bronchiectasis treatment not limited to antibiotics.
For separate exacerbations there must be an unequivocal resolution of symptoms from the first event and >14 days to the commencement of a subsequent event. If this criterion is not met then the exacerbation is counted as a single continuous event.	

20.3.2.2 Collecting signs and symptoms to diagnose exacerbations

The Respiratory and Systemic Symptoms Questionnaire (RSSQ) was originally designed to provide a consistent and harmonised approach for the collection of signs and symptoms relating to the identification of cystic fibrosis related pulmonary exacerbations (Lymp, Hilliard et al. 2009). The questionnaire uses a standardised format to capture various parameters and changes over time in key signs and symptoms. The questionnaire takes the form of an interview script with a number of questions to answer by the patient across various domains. The items captured within the RSSQ cover criteria that are required for both the EMBARC and modified Fuch's definitions and provides an objective way to collect signs and symptoms. A key point of the RSSQ is that it recognises the variability of symptoms between and within individuals and so aims to capture acute changes that vary significantly from day to day fluctuations.

The RSSQ interview script asks patients to describe changes in their symptoms “since their last study visit,” however to satisfy fulfilment of part 2 of the EMBARC definition and the aims of this study, three modified versions of the questionnaire will be required. Data will be captured at three timepoints to obtain measurements at scheduled study visits, the start of an exacerbation and at the resolution of an exacerbation. Therefore, the different versions of the RSSQ will be administered at the following timepoints with following modifications will be made:

1. Scheduled study visit: This will be referred to as the “since the last visit” version.
2. Start of an exacerbation: “since the last visit” is modified to any changes or new symptoms lasting 48 hours or more. This will be referred to as the “symptoms of exacerbation version.”
3. End of exacerbation: “since the last visit” is modified to any changes since the start of antibiotics. This will be referred to as the “end of exacerbation version.”

An additional question will be added to all versions of the RSSQ to facilitate retrospective scoring on the modified Fuch’s definition to cover wheezing (Question 15).The site staff will use the symptoms information collected from the RSSQ results to assess for an exacerbation. Staff will then discuss these findings and the status of the patient with physicians at the site as to whether a prescription for antibiotics or any other change to the patient’s treatment is required and communicate this to the patient. Any such decision will be ultimately based on the clinical judgment of the responsible clinician.. For this sub-study, there will be an internal adjudication panel which will report on the classifications of exacerbations based on EMBARC criteria. The internal adjudication panel will also report on what exacerbations fully qualify for the modified Fuch’s definition.

Table 3: Summary of the RSSQ

RSSQ questionnaire summary						
Questions (answered by patient)	**Possible Answer Choices**					
1. Increased sputum production	Much more	A little more	No change	A little less	Much less	Never experienced symptom
2.1. Sputum thickness	Much thicker	A little thicker	No change	A little thinner	Much thinner	
2.2. Sputum Colour	Worse		No change		Better	
3. Increased chest congestion	Large increase	A little increase	No change	A little decrease	Large decrease	Never experienced symptom
4. New or increased coughing up of blood	Large increase	A little increase	No change	A little decrease	Large decrease	Never experienced symptom
5.1. Intensity of cough	Much harder	A little harder	No change	A little lighter	Much lighter	Never experienced symptom
5.2. Frequency of cough	Much more often	A little more often	No change	A little less often	Much less often	
6. Decreased exercise tolerance	Much harder	A little harder	No change	A little easier	Much easier	
7.Increased dyspnea with exertion	Much more difficult	A little more difficult	No change	A little easier	Much easier	
8. Malaise, fatigue or lethargy	Much more tired	A little more tired	No change	A little more energy	Much more energy	
9.Fever	Yes		No			
10.Weight loss	Large weight gain	A little weight gain	No change	A little weight loss	Large weight loss	
11.Sinus pain and tenderness	Yes		No			
12.Change in sinus discharge	Worse		No change		Better	Never experienced symptom
13.School or work absenteeism (due to illness)	Yes			No		
14.Decreased appetite	Large increase	A little increase	No change	A little decrease	Large decrease	
15. Wheezing (Additional Question)	Large increase	A little increase	No change	A little decrease	Large decrease	Never experienced symptom

20.3.2.3 Forced Expiratory Volume in 1 second (FEV_1):

Measurements of lung function can give an indication of the degree of airflow obstruction and disease severity in bronchiectasis (Pasteur, Bilton et al. 2010). A common lung function test is the forced expiratory volume in 1 second (FEV_1). This is the volume of air that can forcibly be exhaled in one second, after full inspiration and declines with increasing disease severity. A decline in FEV_1 is required for the modified Fuchs therefore an additional instruction for staff to ask the patient to undertake a lung function test at as per the methods. This data will be used to determine the percentage change of FEV_1 over time.

20.3.3 Study Aims:

This study aims to validate and measure the sensitivity of the EMBARC definition for exacerbations in bronchiectasis. The study will compare the criteria in the EMBARC definition to the criteria of a modified Fuch's definition for diagnosing pulmonary exacerbations in bronchiectasis patients. This is the first time the EMBARC definition will be used within in a clinical trial and will be embedded as a sub-study within a UK-wide clinical trial (CLEAR).

Specific objectives of this sub-study will include:

1. To compare the number of pulmonary exacerbations and treatment changes within CLEAR that meet the EMBARC compared to the modified Fuch's definitions.
2. To explore the symptoms (or combinations) that do not meet either criteria for an exacerbation but still result in a change of treatment.
3. To explore changes in the symptoms from the beginning of an exacerbation to its resolution within both definitions.

20.3.4 Methods:

20.3.4.1 Sub-study Design

This sub study will be embedded in CLEAR and will use data directly collected in the trial. It will analyse data specifically related to exacerbations obtained from the four treatment groups.

20.3.4.2 CLEAR Trial Design:

CLEAR is a 2x2 factorial randomised open labelled clinical trial investigating hypertonic saline (HTS) and carbocisteine as mucoactives for bronchiectasis versus standard care. Approximately 380 patients will be randomised to one of the four treatment groups:

- Intervention 1: Standard care and twice daily nebulised HTS (6%) over 52 weeks
- Intervention 2: Standard care and carbocisteine (750mg three times per day until visit 3, reducing to 750mg twice per day)
- Intervention 3: Standard care and a combination of twice daily nebulised HTS (6%) and carbocisteine (750mg three times per day until visit 3, reducing to 750mg twice per day) over 52 weeks.
- Control: Standard care over 52 weeks

20.3.4.3 Patient Inclusion/Exclusion criteria for CLEAR:

Inclusion criteria

i. Diagnosis of BE on CT/HRCT
ii. BE must be the primary respiratory diagnosis
iv. iii. One or more pulmonary exacerbations in the last year requiring antibiotics* . Production of daily sputum**
v. Stable from a respiratory point of view for 14 or more days before randomisation with no changes to treatment***
vi. Willing to continue any other existing chronic medication through the study
vii. Female subjects must be either surgically sterile, postmenopausal or agree to use effective contraception during the treatment period of the trial

*This can include patient reported exacerbations

*** This includes patients who expectorate sputum on a daily basis and/or patients that expectorate sputum on most days but experience difficulty in expectoration on other days. Patients that regularly do not have sputum and do not require to expectorate regularly should not be included in the study.*

**** This inclusion refers to chest treatment however some antibiotics (e.g. for a urinary tract infection (UTI) may have chest coverage and need to be considered.*

Exclusion criteria

i. Age < 18 years' old
ii. Patients with CF
iii. Patients with COPD as a primary respiratory diagnosis
iv. Current smokers, female ex-smokers with greater than 20 pack years and male ex-smokers with greater than 25 pack years
v. FEV1<30%
vi. If being treated with long term macrolides or other long term antibiotic, on treatment for less than 1 month before joining study or planning to stop treatment within one month of joining the study[#]
vii. Patients on regular isotonic saline[##]
viii. Treatment with HTS, carbocisteine or any mucoactives within the past 30 days
ix. Known intolerance or contraindication to HTS or carbocisteine[###]
x. Hypersensitivity to any of the active ingredients or the excipients of carbocisteine

xi. Active peptic ulceration
xii. Any heredity galactose intolerance, the Lapp-Lactase deficiency or glucose-galactose malabsorption
xiii. Patients unable to swallow oral capsules
xiv. Women who are pregnant or lactating
xv. Participation in another Clinical Trial of an Investigational Product within 30 days

[#] If a patient is currently prescribed long term macrolides or other long term antibiotic they must have had no change to their treatment within the 30 days prior to randomisation i.e. if they are prescribed macrolides on a seasonal basis they must not have stopped or started treatment within the 30 days prior to being randomised.

[##] Short term use of isotonic saline for exacerbation management is not an exclusion criteria. In addition patients using isotonic saline as a mixer for colomycin or using saline nasal sprays are not excluded.

[###] Patients who use HTS and/or carbocisteine very occasionally or PRN i.e. during an exacerbation and have not used within 30 days prior to randomisation are not excluded.

20.3.4.4 Data Inclusion for sub study:

Inclusion criteria: patients who contact study staff via telephone at the onset of an exacerbation; completion and recording of RSSQ and concomitant medication form; routine completion of lung function tests remotely. Patient's that provide data relating to symptoms at the beginning and resolution of exacerbations.

20.3.4.5 Data Collection for Exacerbations:

During the treatment period, patients will be asked to telephone the site if they feel they are experiencing symptoms of an exacerbation (i.e. symptoms greater than the day to day fluctuations in symptoms that a patient would normally experience and should ideally be persistent for at least 48 hours). Patients will be advised to wait at least 48 hours from the onset of signs/symptoms before contacting the study team.

Details of the exacerbations will be recorded by a member of the study team by telephone or during an unscheduled visit. Upon patient contact, a member of the study team will undertake the following:

- Identify the patient and what treatment group they are in.
- Complete the RSSQ questionnaire (symptoms of exacerbation version) with the patient.
- Note the date of the start of the symptoms.
- Ask the patient if they did a lung function test on that day and, if not, instruct them to do so using the mySpiroSense spirometer.
- Ask the patient about any new concomitant medications or airway clearance techniques prescribed and update the concomitant medication form and airway clearance technique log, if required.

The results of the RSSQ will be available immediately. After completing the above tasks, the member of the study team will use the RSSQ results to score the exacerbation in the patient's case report form (CRF) according to the EMBARC criteria then discuss the patient reported symptoms (and duration of symptoms) with Investigators or other physicians at the site who will determine whether a prescription for antibiotics is appropriate or any other change to the patient's treatment is required. Any such decision will be ultimately based on the clinical judgment of the responsible clinician.

If the patient has had symptoms for less than 48 hours and has not or is not to be started on any antibiotic treatment, a second follow up telephone call should be arranged with the patient at least 48 hours after the onset of their symptoms and the procedures above

repeated. In the event symptoms are inconsistent with an exacerbation, and/or a face to face visit is required the patient may be asked to make an unscheduled study visit for further examination.

If an exacerbation is diagnosed, the member of the study team will undertake the following:

- Direct the prescription of antibiotics as instructed by the Investigator (type of antibiotic, dose and length of treatment). Arrangements for antibiotics may be directed in different ways depending on local procedures i.e. patients may be directed to commence prophylactic rescue packs held at home, a prescription may be obtained in consultation with their GP or other local arrangements may apply. If antibiotics are not prescribed, the reasons for not doing so should be recorded.
- Record information this alongside any changes in bronchiectasis treatment management on the CRF and concomitant medication form or the airway clearance technique log, if applicable.
- Schedule a follow-up telephone call with the patient to assess for the resolution of the exacerbation. The date for this will be determined by the end of any antibiotic course prescribed to the patient.

The potential end of the exacerbation is defined as the time when the prescribed antibiotic course is completed. At this time point (or up to 14 days later) a member of the study team will call to the patient and:

- Administer the RSSQ questionnaire (end of exacerbation version).
- Ask the patient to complete a lung function test using the mySpiroSense spirometer.
- Review the concomitant medication form and the airway clearance technique log.

The collection of follow-up symptoms will allow exploration of resolution of the exacerbation as well as provide validity of the diagnosis of the exacerbation.If the patient symptoms have not resolved discuss with the investigator who will determine whether a further prescription for antibiotics is required. If further antibiotics are prescribed, arrangements will be made to complete the call for resolution of an exacerbation at the end of their last course of antibiotics. The exacerbation will be counted as one event and the end of this will be when the last antibiotic course is completed.

In the case a patients arrives for a scheduled study visit and feels an exacerbation is imminent but didn’t make contact with the site, a member of the study team will collect the information required regarding the exacerbation and the RSSQ questionnaire (symptoms of exacerbation version) will be administered during their visit. If a schedule study visit coincides with the end of the exacerbation the site will collect the information required and the RSSQ questionnaire (end of an exacerbation version) will be administered during their visit.

Many patients hold prophylactic antibiotics at home but will be directed and regularly reminded at each study visit to contact study staff when feeling signs/symptoms of an exacerbation. This will ensure that antibiotic prescription is directed and recorded through clinical staff.

However patients will be instructed that if they experience symptoms for at least 48 hours during the weekend on a bank holiday they should proceed with taking any rescue pack antibiotics or GP prescribed antibiotics and then report to site staff as soon as possible so that the details can be documented.

Table 3 shows the schedule of assessments to measure for exacerbations remotely versus assessments undertaken at scheduled visits:

Table 4: Schedule of assessments to measure exacerbations

Visit:	**In person at site**	**Remote via telephone**	**Remote via telephone**
Timepoint:	Scheduled study visits within CLEAR	Beginning of exacerbation	End of exacerbation
Visit Window:	Visits 2, 3, 4 and 5	Any time throughout trial when feels symptoms	End of antibiotic course (or up to 14 days)
Review of medications	X	X	X
RSSQ (since last visit version)	X		
RSSQ (symptom of exacerbation)		X	
RSSQ (end of exacerbation)			X
Lung function tests (including FEV_1 spirometry)	X	X	X
Prescribe antibiotics if needed		X	X

Flow diagram of exacerbation management:

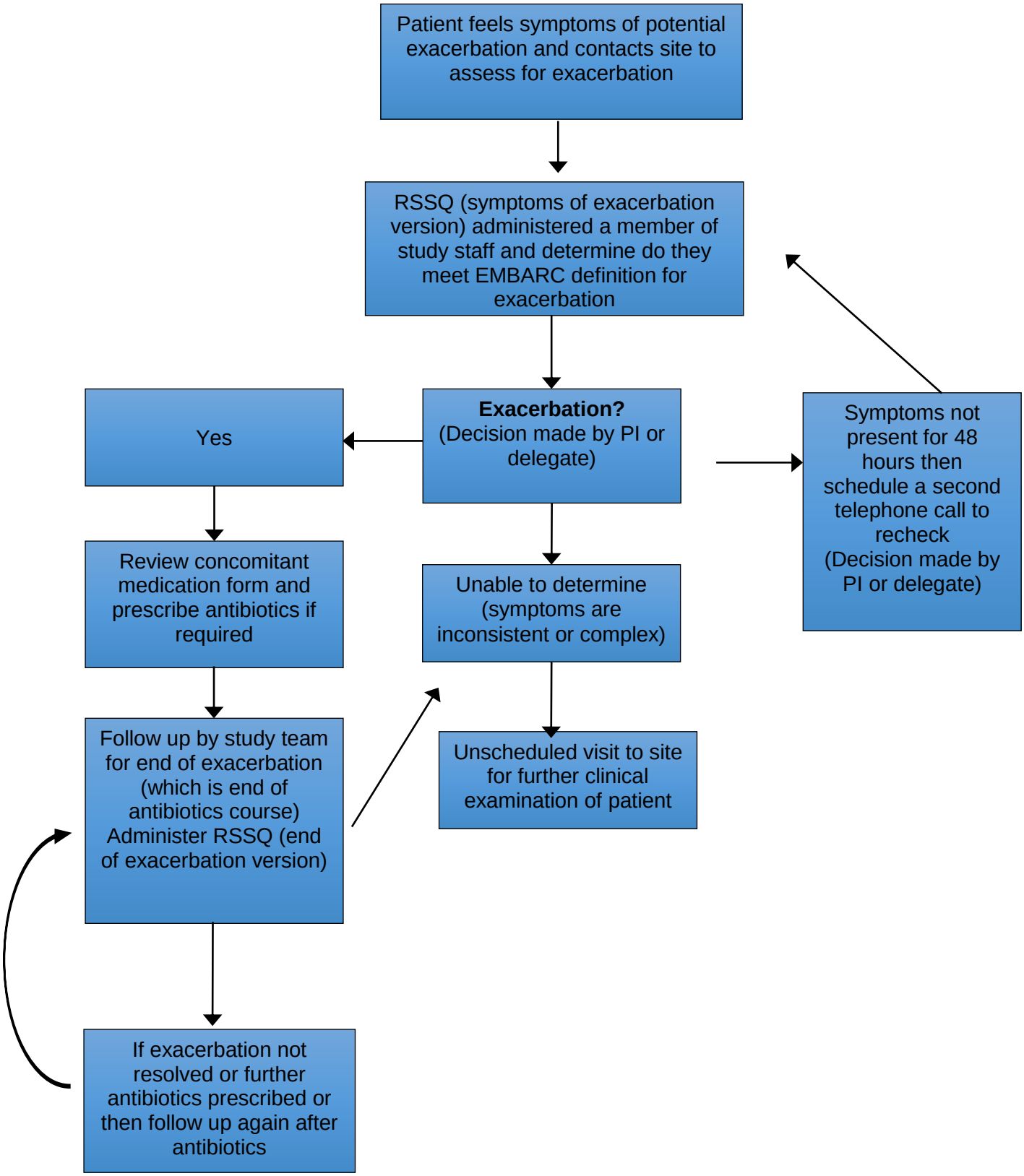


Figure 1: Schematic diagram of remote data collection for exacerbations

20.3.4.6 RSSQ and FEV_1 data collected at other time points during the main trial

In addition to the remotely collected data, RSSQ (since last visit version),spirometry and concomitant medication form will be assessed during CLEAR at the following scheduled patient visits: Visit 1 (Baseline), Visit 2 (Week 2), Visit 3 (Week 8), Visit 4 (Week 26) and Visit 5 (Week 52). The RSSQ (since last visit version) will be used in these main study visits, capturing data on events since the last scheduled visit. The data collected from this version of the RSSQ will explore patients' stability between visits.

Patients in CLEAR will also be directed to undertake weekly spirometry using the MySpiroSense Spirometer outside of study visits so that FEV_1 can be monitored in relation to exacerbations.

20.3.5 Analysis

The EMBARC definition will be used throughout the CLEAR trial and will be used to determine whether patients require antibiotics for exacerbations. However, in cases where a patient fulfils part 3 with either part 1 or part 2 this will be a partially qualifying exacerbation. Those who fully meet the criteria will be classed as having a fully qualifying exacerbation. Those meeting only part 3 will be classed as having another form of exacerbation. Exacerbations fulfilling the modified Fuch's criteria will be calculated retrospectively and will be used only to compare against the EMBARC definition and will not determine antibiotic treatment in the CLEAR trial.

20.3.6 Calculation of EMBARC and Fuchs definitions

The answers from the RSSQ (symptoms of exacerbation version) will be assessed using the methodology outlined in Tables 4 and 5 to ascertain whether signs/symptoms meet the criteria for an EMBARC definition and the modified Fuch's definition.This will be undertaken by external independent adjudication panels Under the Question Number column, if more than one question is li sted with '**and/or**' as a separator, then only one of the questions and respective answers is needed to qualify as a deterioration in that domain. If one of the below answers is given and the time is greater than 48 hours then a deterioration in that domain has occurred.

Table 5: EMBARC scoring system

Domain	Question Number (From RSSQ)	Answers that qualify as deterioration (From RSSQ)	Response that qualify as deterioration present (Yes or No)	Is time >48 hours? (Yes or No)	Deterioration in domain? (Yes or No)
Cough	5.1 *and/or* 5.2	"much harder" *or* "a little harder"			
		"much more often" *or* "a little more often"			
Sputum Volume and/or consistency	1 *and/or* 2.1	"much more" *or* "a little more"			
		"much thicker" *or* "a little thicker"			
Sputum Purulence	2.2	"worse"			
Breathlessness and/or exercise tolerance	7 *and/or* 6	"much more difficult" *or* "a little more difficult"			
		"much harder" *or* "a little harder"			
Fatigue and/or malaise	8	"much more tired" *or* "a little more tired"			
Haemoptysis	4	"large increase" *or* "a little increase"			
				Total deteriorations:	/6

An EMBARC exacerbation will be classified as deterioration in at least three of the six domains.

Table 6: Modified Fuch's scoring system

Domain	Question Number(s) (From RSSQ)	Answers that qualify as deterioration (From RSSQ)	Is time >48 hours (Yes or No)	Deterioration in domain? (Yes or No)
Change in sputum production (consistency, colour, volume, or haemoptysis)	2.1 *and/or* 2.2 *and/or* 1 *and/or* 4	"much thicker" *or* "a little thicker"		
		"worse"		
		"much more" *or* " a little more"		
		"large increase" *or* "a little increase"		
Increased dyspnoea (chest congestion or shortness of breath)	3 *and/or* 7	"large increase" *or* "little increase"		
		"much more difficult" *or* "a little more difficult"		
Increased cough	5.1 *and/or* 5.2	"much harder" *or* "a little harder"		
		"much more often" *or* "a little more often"		
Fever (>38°c)	9	"yes"		
Increased wheezing	15 (Additional Question)	"large increase" or "little increase"		
Decreased exercise tolerance, malaise, fatigue, or lethargy	6 *and/or* 8	"much harder" *or* "a little harder"		
		"much more tired" *or* "a little more tired"		
*FEV_1 decreased 10% from a previously recorded value**	MySpiroSense Spirometer	"yes"	N/A	
			Total deteriorations:	/7

A modified Fuch's exacerbation will be classified as deterioration in at least four of the seven domains.

* *Defined as a previously recorded value from a last stable study visit where possible, as these are the main lung functions we will know are done satisfactorily. If a study visit is not*

considered stable then nearest stable lung function to visit will be considered (Serisier, Martin et al. 2013, Barker, O'Donnell et al. 2014). The percentage decrease will be calculated as:

$$\frac{FEV1\ previously\ recorded - FEV1\ at\ start\ of\ exacerbation}{FEV1\ previoulsy\ recorded} \times 100$$

20.3.7 Timing of analysis and data transfer

Data will be provided for analysis after the completion of an internal pilot study for CLEAR. The pilot study will have target recruitment of 60 patients and will seek to determine recruitment rates, protocol compliance and the quality of data collection. Data from the pilot study will be included in the final analysis of the study providing that no major changes are made between the pilot and the main study.

Anonymised data from the mySpirosense spirometer will be transferred directly by each site Queen's University Belfast for analysis.

20.3.8 Main Statistical Analysis:

An 'Intention to treat' approach will be used throughout CLEAR. Descriptive summaries and cross tabulations will be used to compare the proportion of EMBARC-defined exacerbations that meet the criteria against the modified Fuch's definition and to explore the signs and symptoms that result in a partially qualifying exacerbation. Mean number of exacerbations will be measured from the number of exacerbations per patient over 52 weeks, as defined by each definition. Signs and symptoms that do not meet exacerbation criteria will be summarised. Comparisons will be made between the intervention groups in CLEAR using ANOVA with 95% confidence intervals. Appropriate parametric or non-parametric statistics will be applied to compare mean and median differences in signs and symptoms from the start of an exacerbation to those at the resolution.

20.3.9 References:

BARKER, A.F., O'DONNELL, A.E., FLUME, P., THOMPSON, P.J., RUZI, J.D., DE GRACIA, J., BOERSMA, W.G., DE SOYZA, A., SHAO, L., ZHANG, J., HAAS, L., LEWIS, S.A., LEITZINGER, S., MONTGOMERY, A.B., MCKEVITT, M.T., GOSSAGE, D., QUITTNER, A.L. and O'RIORDAN, T.G., 2014. Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. *The Lancet Respiratory Medicine,* **2**(9), pp. 738-749.

CHANG, A.B. and BILTON, D., 2008. Exacerbations in cystic fibrosis: 4 · Non-cystic fibrosis bronchiectasis. *Thorax,* **63**(3), pp. 269-276.

FINKLEA, J.D., KHAN, G., THOMAS, S., SONG, J., MYERS, D. and ARROLIGA, A.C., 2010. Predictors of mortality in hospitalized patients with acute exacerbation of bronchiectasis. *Respiratory Medicine,* **104**(6), pp. 816-821.

FUCHS, H.J., BOROWITZ, D.S., CHRISTIANSEN, D.H., MORRIS, E.M., NASH, M.L., RAMSEY, B.W., ROSENSTEIN, B.J., SMITH, A.L. and WOHL, M.E., 1994. Effect of Aerosolized Recombinant Human DNase on Exacerbations of Respiratory Symptoms and on Pulmonary Function in Patients with Cystic Fibrosis. *New England Journal of Medicine,* **331**(10), pp. 637-642.

HILL, A., 2017. Pulmonary Exacerbation in Adults with Bronchiectasis: A Consensus Definition from the First World Bronchiectasis Conference. *European Respiratory Journal,* **Draft**(Draft), pp. In Press.

LYMP, J., HILLIARD, K., ROSENFELD, M., KOKER, P., HAMILTON, A. and KONSTAN, M., 2009. Pulmonary Exacerbations in a Phase 2 Clinical Trial of Biil 284 Bs in Cf: Development and Implementation of a Respiratory and Systemic Symptoms Questionnaire (RSSQ). *Pediatric Pulmonology, ,* pp. 288-288.

MAO, B., YANG, J., LU, H. and XU, J., 2016. Asthma and bronchiectasis exacerbation. *European Respiratory Journal,* **47**(6), pp. 1680-1686.

MCSHANE, P.J., NAURECKAS, E.T., TINO, G. and STREK, M.E., 2013. Non–Cystic Fibrosis Bronchiectasis. *American Journal of Respiratory and Critical Care Medicine,* **188**(6), pp. 647-656.

O'DONNELL, A.E., BARKER, A.F., ILOWITE, J.S. and FICK, R.B., 1998. Treatment of Idiopathic Bronchiectasis With Aerosolized Recombinant Human DNase I. *Chest,* **113**(5), pp. 1329-1334.

PASTEUR, M.C., BILTON, D. and HILL, A.T., 2010. British Thoracic Society guideline for non-CFbronchiectasis. *Thorax,* **65**(Suppl 1), pp. i58.

RADEMACHER, J. and WELTE, T., 2011. Bronchiectasis—Diagnosis and Treatment. *Deutsches Ärzteblatt International,* **108**(48), pp. 809-815.

REDONDO, M., FERRI, S. and CHALMERS, J., 2016. Exacerbations of bronchiectasis in adults. *Community Acquir Infect,* **3**(2), pp. 43.

SERISIER, D.J., MARTIN, M.L., MCGUCKIN, M.A., LOURIE, R., CHEN, A.C., BRAIN, B., BIGA, S., SCHLEBUSCH, S., DASH, P. and BOWLER, S.D., 2013. Effect of Long-term, Low-Dose Erythromycin on Pulmonary Exacerbations Among Patients With Non–Cystic Fibrosis Bronchiectasis: The BLESS Randomized Controlled Trial. *JAMA,* **309**(12), pp. 1260-1267.

TSANG, K.W., TAN, K.C., HO, P.L., OOI, G.C., HO, J.C., MAK, J., TIPOE, G.L., KO, C., YAN, C., LAM, W.K. and CHAN-YEUNG, M., 2005. Inhaled fluticasone in bronchiectasis: a 12 month study. *Thorax,* **60**(3), pp. 239-243.

TSANG, K.W.T., HO, P., LAM, W., IP, M.S.M., CHAN, K., HO, C., OOI, C.C.G. and YUEN, K.Y., 1998. Inhaled Fluticasone Reduces Sputum Inflammatory Indices in Severe Bronchiectasis. *American Journal of Respiratory and Critical Care Medicine,* **158**(3), pp. 723-727.

VENDRELL, M., DE GRACIA, J., OLVEIRA, C., MARTÍNEZ, M.A., GIRÓN, R., MÁIZ, L., CANTÓN, R., COLL, R., ESCRIBANO, A. and SOLÉ, A., 2008. Diagnosis and treatment of bronchiectasis. Spanish Society of Pneumology and Thoracic Surgery. *Archivos De Bronconeumologia,* **44**(11), pp. 629-640.

20.3.10 Appendix 1.

20.3.10.1 Original Fuch's criteria:

From the 1994 clinical trial report investigating DNase I for the treatment of cystic fibrosis (Fuchs, Borowitz et al. 1994).

Table 7: Original Fuch's criteria

Criteria for the Fuch's definition	
An exacerbation of respiratory symptoms, prospectively defined in the study, was said to have occurred when a patient was treated with parenteral antibiotics for any 4 of the following 12 signs or symptoms:	
Symptoms, signs or findings	1. Change in sputum 2. New or increased haemoptysis 3. Increased cough; 4. Increased dyspnoea 5. Malaise, fatigue, or lethargy 6. Temperature above 38 °C 7. Anorexia or weight loss 8. Sinus pain or tenderness 9. Change in sinus discharge 10. Change in physical examination of the chest 11. Decrease in pulmonary function by 10 percent or more from a previously recorded value 12. Radiographic changes indicative of pulmonary infection

20.3.11 Appendix 2.

20.3.11.1 O'Donnell version of a modified Fuch's criteria:

The criteria used in the O'Donnell version of a modified Fuch's criteria. First used in a 1998 clinical trial report investigating DNase I for idiopathic bronchiectasis (O'Donnell, Barker et al. 1998).

Table 8: O'Donnell version of a Modified Fuch's criteria

Criteria for the modified Fuch's (O'Donnell version)	
A protocol-defined exacerbation was prospectively defined as abnormalities in 4 of 9 criteria:	
Symptoms, signs or findings	1. Change in sputum production (consistency, colour, volume, or haemoptysis) 2. Increased dyspnoea (chest congestion or shortness of breath) 3. Increased cough 4. Fever (38°c) 5. Increased wheezing 6. Decreased exercise tolerance, malaise, fatigue, or lethargy 7. FEV1 or FVC decreased 10% from a previously recorded value 8. Radiographic changes indicative of a new pulmonary process 9. Changes in chest sounds

20.3.12 Appendix 3.

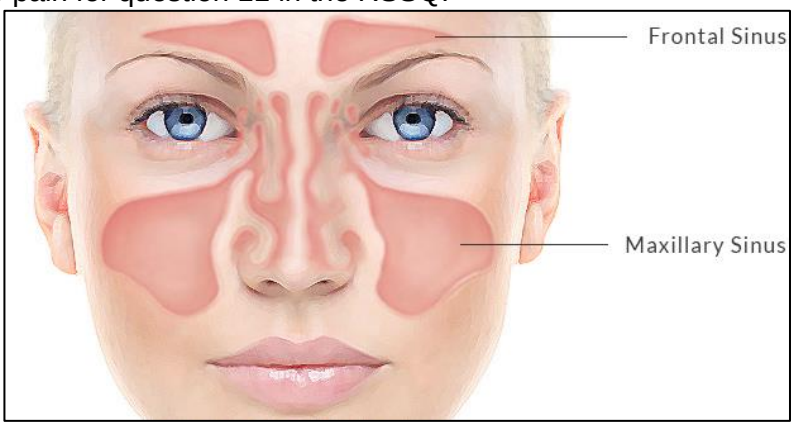
20.3.12.1 Questions relating to FEV1:

1. "Has the patient experienced a decline in FEV_1 > 10% within the last 48 hours?" Answer: Yes or No.
2. “What is the percentage change from the last recorded value?”

20.3.13 Appendix 4.

20.3.13.1 Sinus illustration:

This is the illustration that will be used to inform patients of the location of the sinuses in relation to pain for question 11 in the RSSQ:



20.4 Appendix III: Spirometry Sub-study

20.4.1 Introduction

Measurements of lung function give an indication of the degree of airflow obstruction and disease severity in bronchiectasis (1). Traditionally spirometry is performed when a patient is in clinic under the supervision of a trained healthcare provider and according to standard criteria (2). Technology advances in spirometry equipment have increased opportunities for home monitoring and low-cost portable devices are now available to use outside the clinical setting. Recent studies in various respiratory conditions have found home spirometry monitoring feasible, indifferent to hospital readings and clinically informative (3-6).

PARI has recently released the SpiroSense system which consists of self-calibrating spirometers. The first component of the system is the SpiroSense*Pro* spirometer which is designed for “in clinic” use and lung function measurements are automatically evaluated in accordance with the standards of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) (7). These standards include assessment of:

1. Start-of-test: whether the patient exhaled rapidly and powerfully enough.
2. End-of-test: whether the patient exhaled for long enough.
3. Forced vital capacity (FVC) repeatability: three acceptable measurements must be available in which the difference between the largest and next largest forced vital capacity per second is less than 150ml.
4. Forced expiratory volume in 1 second (FEV1) repeatability: three acceptable measurements must be available in which the difference between the largest and next largest capacity per second is less than 150ml.
5. Calibration: indicates whether the automatic calibration of the device was successful.

Predicted values, percent predicted and Z scores are displayed for SpiroSensePro measurements and use the global lung function 2012 equations (8), with the exception of peak expiratory flow (PEF), FEF25 and FEF50, which use reference values from the European Coal and Steel Community (ECSC/EGKS) in 1993 (9) or the 1987 (10) and 2003 (11) reference value studies by Zapletal.

The second component of the system is the mySpiroSense spirometer. It is a lightweight, portable handheld spirometer designed to be used by patients unsupervised and so allows for spirometry to be conducted at home, outside of clinic visits. The key advantage of the mySpiroSense is that it is easy to use and does not require a high level of technical ability. The mySpiroSense includes a traffic light display system to provide the patient with visual feedback for their latest measurement for a given lung function parameter. For mySpiroSense, a lung function parameter is selected and a predicted value for that patient is stored in the device. A marker appears in the traffic light area of the display screen indicating the percentage of expected value reached: > 80% of expected value shows a green light; 60% - 80% of expected value shows an amber light; < 60% of expected value shows a red light.

Expected values can be set from:

- predicted value based on the 2012 lung function equations.
- personal best values.
- custom values that are freely selectable.

For CLEAR the expected value is set as the patients' personal best of FEV1.

Spirometry data is stored in the mySpiroSense device and can be read directly from the device. It also can be imported into the SpiroSensePro software via the USB interface and be read and displayed alongside SpiroSensePro spirometry data, when the device is brought into clinic.

This sub-study will explore the use of mySpiroSense for remote spirometry during periods of stability (weekly measurements and measurements on the morning of study visits) and at the start and end of exacerbations in an adult bronchiectasis population.

20.4.2 Aims

This sub-study will aim to:

1. Explore any difference in lung function parameters of home spirometry compared to spirometry completed on the same day in clinic.
2. Explore patient adherence to weekly home spirometry.
3. Explore the quality of home spirometry.
4. Explore changes in spirometry at the start of an exacerbation and on resolution of an exacerbation and if lung function can be used as a predictor for exacerbations.

20.4.3 Methods

This methodology is embedded within the CLEAR trial.

Spirometry will be conducted at the following times:

- Weekly: Throughout the trial all patients will be advised to complete spirometry at home on a weekly basis using the mySpiroSense. They will be asked to conduct 3 readings around the same time of day (and where possible post morning airway clearance treatments).
- On the day of study visits: Patients will be asked to complete home spirometry on the morning of scheduled visits using the mySpiroSense before coming into clinic for study visits. Patients will then complete clinic spirometry during their study visit using the SpiroSensePro device under the supervision of a clinician.
- At the beginning of an exacerbation: Upon a patient telephone call suspecting an exacerbation, the study staff will instruct patients to complete a home lung function test using the mySpiroSense.
- At end of an exacerbation: Upon a patient telephone call at end of an exacerbation, the study staff will instruct patients to complete a home lung function test using the mySpiroSense.

The mySpiroSense lung function readings are retained in the memory of the device. Patients will bring their mySpiroSense to each study visit and the data will be

imported to computers on site. The SpiroSensePro software will display the measurements for the patient as 'thumbnails' in the display area sorted in descending chronological order. The background colours of the individual thumbnails identify the measurement types: Green thumbnails taken with a mySpiroSense, purple thumbnails taken with a SpiroSensePro and blue is a bronchodilation test. Local site staff will send pseudonymised spirometry data using a secure method in line with local and national requirements for data protection and security to the research teams for analysis.

20.4.4 Analysis Plan

Spirometry parameters will include FEV1, FVC and FEF25-75%. The comparison of home and clinic spirometry (mySpiroSense versus SpiroSensePro measurements) will be analysed using the Bland–Altman method. This will be a comparison on visit days and the best of three measurements will be used in the statistical analysis. Appropriate descriptive statistics will be used to summarise adherence to weekly home spirometry and level of quality of home spirometry data. Parametric/non-parametric statistics will be applied to compare changes in spirometry at the start and end of exacerbations. A time dependent Cox proportional hazards model will be used to investigate the impact of changes in lung function on the likelihood of an exacerbation.

20.4.5 Discussion

With the rising cost and duration of clinical trials the validation and use of home spirometry will also aid the more pragmatic design of respiratory trials. Less scheduled visits and subsequent assessments will reduce the overall burden for both patients and clinicians. Technological remote or in-home assessments incorporated into clinical trials are likely to make trials more efficient in terms of cost, duration, adherence, recruitment and retention (12, 13). The results from this sub-study will determine whether home spirometry for bronchiectasis patients is feasible. It will explore agreement between supervised spirometry performed in clinic and home spirometry performed independently by patients. In addition, this study will explore changes in home spirometry at the beginning and end of exacerbations.

20.4.6 References

1. Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-CFbronchiectasis. Thorax. 2010;65(Suppl 1):i58.
2. Moore VC. Spirometry: step by step. breathe. 2012;8(3):232.
3. Russell A, Adamali H, Molyneaux PL, Lukey PT, Marshall RP, Renzoni EA, et al. Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis. American journal of respiratory and critical care medicine. 2016 Oct 15,;194(8):989-97.
4. Moor CC, Wapenaar M, Miedema JR, Geelhoed JJM, Chandoesing PP, Wijsenbeek MS. A home monitoring program including real-time wireless home spirometry in idiopathic pulmonary fibrosis: a pilot study on experiences and barriers. Respiratory Research. 2018;19(1):105.
5. Rodriguez-Roisin R, Tetzlaff K, Watz H, Wouters EF, Disse B, Finnigan H, et al. Daily home-based spirometry during withdrawal of inhaled corticosteroid in severe to very severe chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2016 -8-22;11:1973-81.
6. Shakkottai A, Nasr SZ. The Impact of Frequent Home Spirometry on Medication Adherence, Health Outcomes and Quality of Life Among Adolescents with Cystic

Fibrosis. In: C67. SUPPURATIVE LUNG DISEASES IN CHILDREN. American Thoracic Society; 2017. p. A6136.
7. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319.
8. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012 Dec;40(6):1324-43.
9. Laszlo G. European standards for lung function testing: 1993 update. Thorax. 1993;48(9):873-6.
10. Zapletal A, Šamánek M, Paul T. Lung Function in Children and Adolescents. Karger; 1987.
11. Zapletal A, Chalupová J. Forced expiratory parameters in healthy preschool children (3-6 years of age). Pediatr Pulmonol. 2003 Mar;35(3):200-7.
12. Hirsch IB, Martinez J, Dorsey ER, Finken G, Fleming A, Gropp C, et al. Incorporating Site-less Clinical Trials Into Drug Development: A Framework for Action. Clin Ther. 2017 May;39(5):1064-76.
13. Anderson D, Fox J, Elsner N. Transforming the future of clinical development. Deloitte Insights. 2018 Feb:1-25.

20.5 Appendix IV: Optimising Recruitment and Retention: Implementing Studies Within A Trial (SWATs) with the CLEAR clinical trial

Table of Contents

20.5.1 Introduction

Clinical trials depend on the willingness of healthcare professionals and patients or members of the public who dedicate their time and commitment to participate in these studies.

Clinical trials require the successful recruitment of an adequate number of patients (Fisher, Hessler et al. 2012) and if the required levels of patient recruitment and their subsequent retention are not met, this has implications for the trial's statistical power, likelihood of publication and internal and external validity (Glasgow, Eakin et al. 1996). Recruiting inadequate numbers of patients can place a financial strain on the research funder and the study might overrun, potentially influencing investments from research councils and governments for future research (Treweek, Lockhart et al. 2013). Therefore, achieving appropriate numbers of participants is crucial.

However, despite the importance of achieving high levels of patient recruitment and retention, very few clinical trials in bronchiectasis patients have investigated the impact of recruitment strategies, meaning that specific challenges for recruiting these patients are uncertain. We will contribute to filling this gap in this study.

One approach for testing the effectiveness of different recruitment or retention methods is to 'nest' a methodology study within an ongoing trial, using a SWAT (Study Within A Trial) design. The SWAT concept aims to highlight and identify a variety of

methodology strategies that would improve clinical research. It includes approaches that randomly allocate trial participants to two or more differing strategies. Examples of SWAT studies are available on The Northern Ireland Network for Trials Methodology Research website (QUB, 2017).

In many clinical trials outside of primary care, it is standard practice for patients who are potentially eligible to be sent or given an invitation letter by their consultant or hospital clinic; and this is usually one of the first stages in recruitment for bronchiectasis patients. The person signing this invitation letter may act as part of the persuasion strategy to encourage a patient to volunteer for the trial and different methods of personalisation, such as hand-written signatures from the consultant or a member of the clinical research team might have different effects on patient recruitment. Even if these effects are moderate, any boost in recruitment might shorten the trial, save resources and lead to a faster answer to the clinical question posed by the trial. As an example, an ongoing SWAT is exploring whether the gender of the person signing the invitation letter affects recruitment to a prospective cohort study (Maguire, Burns et al. 2015).

The inclusion of a photograph in the introductory material for a clinical trial might also have an effect on responses and patient recruitment. For instance, patients might be more willing and comfortable to participate in a study if a friendly photograph of a doctor-patient interaction is shown on the invitation letter.

Furthermore, after the patient has been recruited, it is important to ensure that their relevant outcomes are measured and effective strategies are needed to encourage their retention in the trial. An incentive such as the use of a hand-written thank you card may be a simple gesture of kindness, and might, in turn, be a way to improve patient retention. Patients who receive a thank you card after each study visit may feel more valued and appreciated, and may be more inclined to attend future visits.

Finally, regardless of any effect on overall response rates, the individual signing the invitation letter, the inclusion of a photograph and use of thank you cards might encourage patients to respond more promptly and participate longer in the trial.

20.5.2 Project Aims:

The aim of this project is to explore the effect of methods used to optimise recruitment and retention. The specific objectives for this research are:

- To explore if the nature of the signature and inclusion of a photograph on the invitation letter or introductory material given to potential participants impacts on their recruitment to the trial.
- To explore if giving enrolled participants a thank you note at the end of each study-related visit impacts on their retention in the trial.

20.5.3 Methods:

These objectives will be met by implementing three SWATs in a bronchiectasis clinical trial (CLEAR) within various hospital sites across the United Kingdom.

20.5.4 SWATs to be implemented:

SWATs have been submitted to the SWAT Repository Store of the Northern Ireland Methodology Hub and details can be found on the webpage (QUB, 2017). SWAT A is a variation of SWAT ID 3 on the repository store whilst SWAT B is SWAT ID 53 and SWAT C is SWAT ID 54. The first two SWATs (A & B) are focused on the recruitment stage of the trial, whereas the third SWAT (C) is focused on the retention of enrolled patients.

The specific details of the SWATs are:

A. Nature of the signature on the invitation letter in the trial recruitment pack.
   -Interventions in this SWAT:
   I. Invitation letter is personally signed, using wet ink, by the local principal investigator (PI).
   II. Invitation letter is generically signed and printed electronically as “The CLEAR Trial Team”

B. Inclusion of a generic doctor-patient photograph on the invitation letter (Supplement 1).
   -Interventions in this SWAT:
   I. Invitation letter includes a generic doctor-patient photograph
   II. Invitation letter does not include a doctor-patient photograph

C. Giving trial participants a thank you note/card after each study visit.
   -Interventions in this SWAT:
   I. Personalised thank you card, including the patient’s name is signed, using wet ink, by the study staff
   II. Generic thank you card, not including patient’s name is generically signed and printed electronically as “The CLEAR Trial Team”
   III. No thank you card

20.5.5 Background of CLEAR:

The CLEAR trial is a UK wide, 2x2 factorial randomised trial investing hypertonic saline (HTS) and carbocisteine for the treatment of bronchiectasis.

20.5.6 Participating Sites:

At least 16 sites will participate in the CLEAR trial. All are NHS hospitals in the United Kingdom with access to a bronchiectasis population. A number of these participating sites will implement the SWATs, depending on site-specific feasibility.

20.5.7 Overall CLEAR Recruitment Strategy:

The participating sites will use common methods for the recruitment of potential participants. This primarily involves directly approaching potential participants who are regularly attending the clinic or have been referred. Once a potential participant is identified and approached, they will be told about the CLEAR trial and given a recruitment pack that contains an invitation letter, patient information sheet and informed consent form. Potential participants are screened from databases and in this instance the recruitment pack is posted to their home address including patients that have previously indicated that they are interested in the study. After being given this recruitment pack, the patient will be able to assimilate the information and ask the study team any initial questions. In addition to this direct approach, patient electronic databases may be screened for eligible participants and they will then be followed up by the study team. If a patient wishes to enrol in the CLEAR trial they will arrange a visit to their recruiting site, clarify any further queries and complete the informed consent form in the presence of a study staff member.

20.5.8 SWATs A and B

Patients were recruited to SWAT A and SWAT B from 27/06/2018, to 21/09/2021. SWAT A and SWAT B are no longer active. Information on SWAT A and SWAT B is retained in Protocol V6.0 for reference purposes.

20.5.8.1 Outcome Measures:

1. Primary outcome: Proportion of recipients of each of the four the invitation letters who join the CLEAR trial.

2. Secondary outcome: Proportion of recruited participants who received each of the four invitation letters who remain enrolled in the CLEAR trial.

20.5.8.2 Design and Implementation of these SWATs:

A 2x2 factorial randomised approach will be used for SWATs A and B to allow a simultaneous comparison of the interventions. The four possible combinations of invitation letter are shown in the table below:

SWATs A and B will be implemented for those generic recruitment packs that are handed to potential participants in person at clinics and recruitment packs that are posted to patients.

Sites that participate in the SWATs will be asked whether to participate prior to enrolment and to estimate their expected recruitment numbers. The local PI using wet ink will sign a related number of invitation letters at appropriate time points including the SIV.

Equal numbers of the four types of recruitment pack will be prepared per site based on recruitment estimates, with each pack being given a unique Pack Identifying Number located on the envelope. Packs will be randomised into bundles using a block size of 8, so that each bundle of 8 contains two of each type of invitation letter. The bundles will be distributed to sites with instructions not to alter the sequence of the packs in the bundles or the order of the bundles.

When giving recruitment packs to a potential participant in person, site staff will take the topmost pack from the bundle so that they are handed out in the correct sequence. Before the recruitment pack is given to a patient, the Pack Identifying

Number will be recorded against the relevant Patient Identification Number on the screening log. If a site uses more than one member of staff to recruit at a time, the packs will be split into two or more piles, with packs then being tracked for sequential use from the bundles in each of these piles. The unique pack identifying numbers will be used to link individuals who do or do not enrol into the trial with the type of recruitment pack they were given.

When posting a recruitment pack to the patient, sites will address the envelope the recruitment pack is contained in to the potential participant.

Should a site have limited numbers of recruitment packs left, they will request further packs and if they exhaust their supply will default to using the standard CLEAR invitation letters until further pack arrives. Logging and tracking of any standard invitation letters will not occur and will not be used in the analysis. Sites not participating in SWATs will use the standard invitation letter throughout the duration of CLEAR.

20.5.8.3 Analysis:

The primary analysis will compare the proportion of participants recruited to the CLEAR trial depending on the type of recruitment pack they received. Secondary analyses will examine retention in CLEAR and the extent/duration of the recruited person's participation.

Schematic Diagram

20.5.9 SWAT C

20.5.9.1 Outcome Measures:

1. Primary outcome: Proportion of participants, in each of the three groups, who remain enrolled in the CLEAR trial.

2. Secondary outcomes: Duration of time that participants, in each of the three groups, who remain in the CLEAR trial before they withdraw.

20.5.9.2 Design and Implementation:

Enrolled patients will be randomised using their Subject ID to either receive a generic thank you card (code 01), a personalised thank you card (code 02) or no thank you card (code 03) at the end of every study visit they attend. The relevant numerical code will be recorded on the patient's case report form for tracking purposes. Sites not participating in SWATs will be coded as N/A. The message within the cards will thank patients for their time in attending their visit. If patients are randomised to receive a generic card the study staff leading the visit will not add anything to the message. If patients are randomised to receive a personalised thank you card, the study staff member leading that visit will handwrite the patients name and then handwrite their own name to sign the card. If a patient has been randomised to receive any of the thank you cards, the relevant card will be prospectively inserted into their study file before each scheduled visit. The cards will be given to the patients by the site staff at the end of visits 1-5 as shown below:

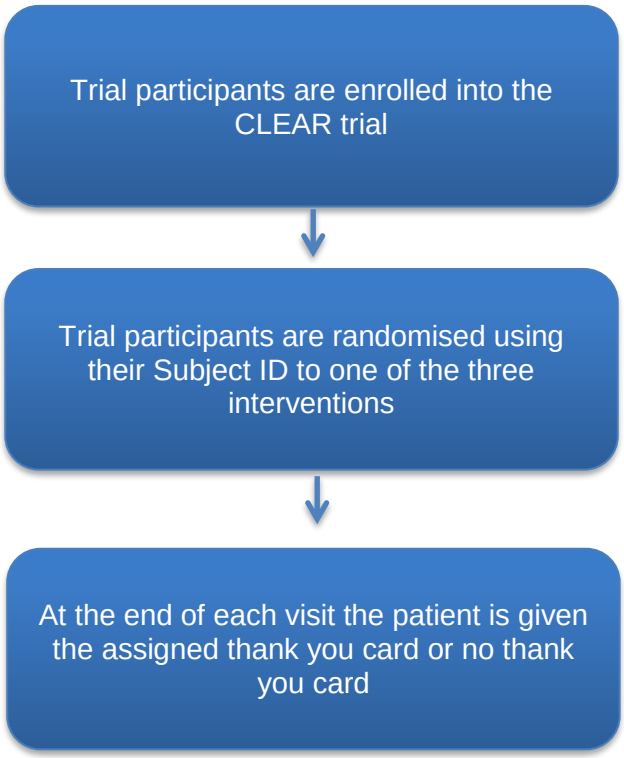
Visit Number:	1	2	3	4	5
Visit Time:	Base-Line	Week 2	Week 8	Week 26	Week 52

Should a patient withdraw from the trial, record the date of withdrawal in the source data.

20.5.9.3 Analysis:

This third SWAT will compare retention between the three groups and the total time participants spend in the CLEAR trial**.**

20.5.9.4 Schematic Diagram:



References:

, QUB, 2017. Available: https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/ [10 MAY, 2017].

FISHER, L., HESSLER, D., NARANJO, D. and POLONSKY, W., 2012. AASAP: a program to increase recruitment and retention in clinical trials. *Patient Education and Counseling*, **86**(3), pp. 372-377.

GLASGOW, R.E., EAKIN, E.G. and TOOBERT, D.J., 1996. How Generalizable are the Results of Diabetes Self-Management Research? The Impact of Participation and Attrition. *The Diabetes Educator*, **22**(6), pp. 573-585.

MAGUIRE, L., BURNS, F. and CLARKE, M., 2015. The NICOLA recruitment trial (NICOLA-RT): can you improve recruitment by making zero cost amendments to the invitation letter? *Trials*, **16**(2), pp. P106.

TREWEEK, S., LOCKHART, P., PITKETHLY, M., COOK, J.A., KJELDSTRØM, M., JOHANSEN, M., TASKILA, T.K., SULLIVAN, F.M., WILSON, S., JACKSON, C., JONES, R. and MITCHELL, E.D., 2013. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ open*, **3**(2), pp. e002360.

20.5.10 Supplement 1: Generic doctor-patient photograph

20.6 Appendix V: Treatment of BE patients with HS and/or CS will lead to reductions in sputum viscosity/elasticity, inflammation and bacterial abundance

20.6.1 Research question:

Does treatment with hypertonic saline and/or carbocisteine decrease sputum viscosity, elasticity, inflammation and bacterial load in the lungs of patients with bronchiectasis?

20.6.2 Aims and objectives

We will assess sputum samples obtained from the CLEAR trial for reductions in sputum viscosity and elasticity, reductions in inflammation and changes in bacterial abundance/composition for patients receiving HS and/or CS. Any changes in these sputum indices will be related to reductions in exacerbation frequency.

20.6.3 Primary Objective:

The primary objective is to measure sputum viscosity (G') and elasticity (G'') (which combined give a single summary measure of sputum viscoelasticity called the yield stress, T_c) at the initial visit and 2 weeks following commencement of treatment with HS and/or CS.

20.6.4 Secondary Objectives:

1). Measure sputum viscoelasticity (yield stress, T_c), at 8 weeks following commencement of treatment with HS and/or CS.
2). Evaluate sputum inflammation as measured by IL-6, IL-8 and 8-isoprostane levels at the initial visit, 2 and 8 weeks following commencement of treatment with HS and/or CS.
3). Evaluate sputum bacterial load/composition at the initial visits, 2 and 8 weeks following commencement of treatment with HS and/or CS.

20.6.5 Primary outcome (based on sample measurements)

The primary outcome measure at the initial visit and 2 weeks post commencement of treatment will be:

- Sputum viscosity (G')
- Sputum elasticity (G'')
- Yield stress T_c (derived from G' and G'')

20.6.6 Secondary outcome (based on sample measurements)

The secondary outcome measure at the initial visits and 2 weeks post commencement of treatment will be:

- Sputum bacterial density (qPCR)
- Sputum bacterial composition (Next generation sequencing – NGS)
- Sputum IL-6
- Sputum IL-8
- Sputum 8-isoprostane

The secondary outcome measure at 8 weeks post commencement of treatment will be:

- Sputum viscosity (G')
- Sputum elasticity (G'')
- Yield stress T_c (derived from G' and G'')
- Sputum bacterial density (qPCR)
- Sputum bacterial composition (Next generation sequencing – NGS)
- Sputum IL-6
- Sputum IL-8
- Sputum 8-isoprostane

The overall aim of this study is to provide mechanistic insight into the action of HS and/or CS in bronchiectasis

20.6.7 Research design

The proposed study is a prospective, multi-centre, exploratory, cohort observational study embedded within the CLEAR trial. It will be conducted in a minimum of 14 Respiratory Clinics participating in CLEAR.

20.6.8 Target Population

We will aim to recruit 72 patients (see sample size calculation below) sequentially enrolled to the CLEAR trial, at sites participating in the main CLEAR Trial. All consecutive patients recruited to CLEAR will be approached to participate in the current study. The PDRA recruited to carry out sputum lab analysis (rheometry, bacterial and inflammation) will be blinded to the treatment allocation (HS, CS, HS+CS and standard care alone) of each sample

20.6.9 Inclusion criteria

i. Diagnosis of BE on CT/HRCT

ii. BE must be the primary respiratory diagnosis

iii. One or more pulmonary exacerbations in the last year requiring antibiotics*

iv. Patients who are at least 80% adherent in their use of HS and/or CS

v. Production of daily sputum

vi. Stable for 14 or more days before first study visit with no changes to treatment

vii. Willing to continue any other existing chronic medication through the study

viii. Female subjects must be either surgically sterile, postmenopausal or agree to use effective contraception during the treatment period of the trial

* This can include patient reported exacerbations.

20.6.10 Exclusion criteria

i. Age < 18 years' old

ii. Patients with CF

iii. Patients with COPD as a primary respiratory diagnosis

iv. Current smokers, female ex-smokers with greater than 20 pack years and male ex-smokers with greater than 25 pack years

v. FEV1<30%

vi. If being treated with long term macrolides, on treatment for less than 1 month before joining study

vii. Patients who are less than 80% adherent in the use of HS and or CS

viii. Patients on regular isotonic saline.

ix. Treatment with HS, CS or any mucolytics within the past 30 days

x. Known intolerance or contraindication to HS or CS.

xi. Hypersensitivity to any of the active ingredients or the excipients of CS

xii. Active peptic ulceration

xiii. Any heredity galactose intolerance, the Lapp-Lactase deficiency or glucose-galactose malabsorption.

xiv. Patients unable to swallow oral capsules.

xv. Women who are pregnant or lactating

xvi. Participation in another Clinical Trial of an Investigational Product within 30 days

20.6.11 Procedures

Patients will be screened and recruited according to CLEAR trial procedures. Randomisation will ensure balance of baseline characteristics during the study.

Collection of samples:

Sputum will be collected at 3 time-points during the study – at the initial visit when patients are randomised to treatment (baseline), week 2 after commencement of treatment and week 8 after the commencement of treatment.As sputum collection is not currently part of the CLEAR trial, an amendment to ethics will be required in order to facilitate collection of sputum. These timelines (baseline, week 2 and week 8) correspond with the visit timeline outlined in the CLEAR protocol and will not require additional visits for trial participants.

20.06.12 Statistical analysis

The primary analysis will be on the per-protocol population as we want to determine differences between groups of patients who adhered to the study drugs and at a significance level of 0.05 unless adjustment for multiple testing is needed.

Primary objective: The primary objective is to measure sputum elasticity (G') and viscosity (G'') (which combined give a single summary measure of sputum viscoelasticity called the yield stress, T_c) at the initial visit and 2 weeks following commencement of treatment with HS and/or CS.

Analysis:

Sputum will characterized by its elastic (G') and viscous (G") moduli in order to determine the yield stress value, Tc, a marker of sputum motion. A high $T_{c,}$ indicates a greater amount of obstruction in the sample and a lower $T_{c,}$ indicates a decreased amount of obstruction in the sample. We will assess the sputum elasticity, viscosity and yield stress in sputum samples obtained from all 4 patient cohorts on the CLEAR trial at the initial visit and 2 weeks. Comparisons will be made between the groups using Analysis of Covariance (ANCOVA) (and post-hoc tests if significant differences are identified) will be used to detect difference in means adjusting for baseline values.

Secondary objectives:

1). Measure sputum elasticity (G') and viscosity (G'') (and yield stress, $T_{c)}$, at 8 weeks following commencement of treatment with HS and/or CS.2). Evaluate sputum inflammation as measured by IL-6, IL-8 and 8-isoprostane levels at the initial visit, 2 and 8 weeks following commencement of treatment with HS and/or CS.

3). Evaluate sputum bacterial load/composition at the initial visit, 2 and 8 weeks following commencement of treatment with HS and/or CS.

Analysis:

Differences in sputum elasticity (G'), viscosity (G") and yield stress value, T_c, will be determined at 8 weeks, as for the primary objective analysis, and compared to sample measurements at baseline (before commencement of treatment). Further comparisons will be made between the groups using ANCOVA. For bacterial abundance, and IL-6, IL-8 and 8-isoprostane measurements, comparisons will be made to sample measurements at baseline (before commencement of treatment). Further, comparisons between the groups will also be made using ANCOVA.

Bacterial density and microbiota data will be combined with clinical and biomarker data and analysed using network and linear regression (univariate and multivariate regression modelling) and principal component analysis (PCA). Intra-sample similarities/differences will be assessed through a number of ecological indices, such as sample richness (number of observed taxa), diversity (Shannon-Wiener index), community evenness and dominance. Factors explaining differences among microbial communities will be assessed through principal coordinates analysis (PCoA) of UniFrac distance values (β-diversity measure used for comparing biological communities based on phylogenetic distance information), with the axes scaled by the percentage of the variance. The amount of variation explained will be presented for the first 2 principal coordinates. Furthermore, potential overlap of taxa within communities will be assessed through the construction of co-occurrence/ co-exclusion networks (31). The relationship between presence/absence of potentially pathogenic bacteria, the main ecological indexes of the metacommunity (i.e., taxonomic richness, Shannon-Wiener index of diversity, evenness, dominance) and 1º/2º endpoints will be assessed by regression analysis (coefficients of determination; residuals; significance) and by the correlation between relevant variables. Statistical analyses and graphical representations will be carried out in GraphPad Prism (version 8.00) and R version 3.4.2. (https://www.r-project.org/).

We will investigate associations between the rheometry, microbiology and inflammatory data and the clinical outcomes in CLEAR such as mean number of exacerbations and lung function. Depending on the nature of the data, we will use appropriate methods of regression analysis and calculate estimates of effect and 95% Confidence Intervals to analyse the data and correlate between the study and the CLEAR outcomes. A detailed Statistical Analysis Plan (SAP) will be written by the trial statistician and approved by the independent DMEC prior to analysis

20.6.13 Ethics / Regulatory approvals

The addition of this study to the CLEAR trial procedures will involve the collection of additional sputum samples at 3 sampling points only which are already scheduled time-points in the CLEAR trial. For this reason, we aim to conduct this study seeking amendments to the existing CLEAR patient information sheet and consent form. This

amendment will be requested of the research ethics committee (REC) who approved the original application (North East – Tyne & Wear South Research Ethics Committee) if successful in this application.