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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

Submission date	**Recruitment status**	[_] Prospectively registered
25/06/2018	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
06/07/2018	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
06/08/2025	Respiratory	[X] Record updated in last year

Plain English summary of protocol

Background and study aims

Bronchiectasis is a condition where the lungs' airways become widened, leading to a build-up of mucus that can make them more vulnerable to infection. Patients with bronchiectasis suffer from a persistent cough, daily sputum (saliva and mucus) production and recurrent exacerbations, affecting quality of life. This study is concerned with sputum production and exploring which combinations of treatments (hypertonic saline (HTS) and carbocisteine) might help patients bring up their sputum more easily. HTS is salty water that is delivered into the airways via a nebuliser, which converts it into a mist. This treatment takes ten minutes. Carbocisteine is taken as a capsule. Research has shown that these treatments can make it easier for patients to cough up sputum, resulting in potentially fewer exacerbations and hospital admissions, which could improve quality of life for people with bronchiectasis. These treatments are currently used in clinical care but there is not enough evidence to recommend them as part of standard care. The aim of this study is to find out whether HTS and/or carbocisteine result in better outcomes than usual care in patients with bronchiectasis.

Who can participate?

Patients with bronchiectasis

What does the study involve?

Participants are randomly allocated to one of four combinations of treatments: HTS and standard care, carbocisteine and standard care, a combination of HTS and carbocisteine with standard care, and standard care alone. Participants have to attend six additional appointments as part of the study over a 2-year period with five in year one. At the start of the study, information is collected about participants' smoking status, bronchiectasis characteristics, medications, medical history, exacerbation history, antibiotic use, and any airway clearance techniques used. A physical exam, vital signs and urine pregnancy test are completed. A

questionnaire is completed with patients to explore any respiratory symptoms they may be experiencing since their last clinic visit. A lung function test is also performed and a range of health-related quality of life questionnaires are completed. At subsequent visits, lung function tests are repeated, exacerbation history is explored, vital signs are obtained and questionnaires are completed again. The nebulizer that patients use to deliver the hypertonic saline can record data about how the patient uses the nebuliser. This usage data is not reviewed with the patient until after they have completed the first year of the study. All patients are also be given a spirometer to perform lung function tests at home on a weekly basis. In addition, patients are asked to use their spirometers at the start of a suspected exacerbation. Patients are asked to bring their spirometer to each study visit. At the 52-week visit the patient is also asked to complete a questionnaire about using the spirometer and nebuliser. Follow-up at 104 weeks collects information about the patient's quality of life, any exacerbations they have had or any antibiotics they have taken for exacerbations. If the patient is already taking part in studies that are currently collecting information on bronchiectasis patients are asked for permission to use this information. Otherwise they are invited to the study site for an additional visit.

What are the potential benefits and risks of participating?
Carbocisteine may help reduce exacerbations and hospitalisations for people with bronchiectasis, improving their overall quality of life. All participants in the study receive a device to test their lung function at home and are also monitored regularly throughout the study. This may improve the overall care they receive through earlier recognition of exacerbations. Ultimately it is hoped that this research will help guide the treatment of bronchiectasis for people in the future and this may benefit patients in the long term outside of the study. Depending on the group allocation, a participant's treatment may be altered. A small number of people experience minor side effects from nebulising HTS such as wheezing, but the likelihood of this will be minimised by patients completing a drug response assessment on entry into the study. A small number of patients experience some minimal side effects (stomach discomfort, vomiting, skin rashes and allergies) associated with carbocisteine. Lung function procedures may cause the participant to cough, experience shortness of breath, or feel lightheaded, but there is no pain expected with these tests. Treatment will be provided if this occurs. This study will take place outside of the normal clinical management of participants. Participants will be required to attend up to six additional visits lasting about 2 hours. Appointments will be scheduled at a time convenient to participants, where possible in an attempt to minimise this burden.

Where is the study run from?
Belfast City Hospital (UK) (lead centre)

When is the study starting and how long is it expected to run for?
July 2017 to September 2024

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
Prof. Judy Bradley
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Study website
https://nictu.hscni.net/service/clear-trial/

Contact information

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Additional identifiers

EudraCT/CTIS number
2017-000664-14

IRAS number
214254

ClinicalTrials.gov number
NCT04140214

Secondary identifying numbers
CPMS 37574; 16178SE-AS, IRAS 214254

Study information

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

Acronym
CLEAR

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

Ethics approval required
Old ethics approval format

Ethics approval(s)
North East – Tyne & Wear South Research Ethics Committee, 20/12/2017, ref: 17/NE/0339

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Bronchiectasis

Interventions
Current interventions as of 06/08/2025:
Treatment allocation will be assigned using an automated randomisation process. 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, >3 times) and based on current use of macrolides (yes, no).

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 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
Intervention 4: Control: standard care over 52 weeks

The study treatment period is 52 weeks.

Previous interventions:
Treatment allocation will be assigned using an automated randomisation process. 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, >3 times) and based on current use of macrolides (yes, no).

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Intervention 4: Control: standard care over 52 weeks

The study treatment period is 52 weeks, after which follow-up will take place at week 104.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Hypertonic saline, carbocisteine

Primary outcome measure
Mean number of exacerbations over 52 weeks; exacerbations diagnosed as they occur via interview with patients and completion of the Respiratory and Systemic Symptoms questionnaire (RSSQ)

Secondary outcome measures
1. Disease-specific health-related quality of life (HRQoL) at 52 weeks measured using the respiratory symptoms domain of quality of life with bronchiectasis (QoL B) questionnaire completed at baseline, 2 weeks, 8 weeks, 26 weeks and 52 weeks
2. Time to next exacerbation post-randomisation measured in days, with exacerbations diagnosed as they occur via interview with patients and completion of the RSSQ
3. Number of days of antibiotics related to exacerbations over 52 weeks assessed via interview with patients at 2, 8, 26 and 52 weeks
4. Generic health-related quality of life (HRQoL) measured using the EQ-5D-5L questionnaire at baseline, 2 weeks, 8 weeks, 26 weeks and 52 weeks
5. Health Service use over 52 weeks assessed via completion of a questionnaire completed at baseline, 2 weeks, 8 weeks, 26 weeks and 52 weeks
6. Quality Adjusted Life Years (QALYs) over 52 weeks calculated by assessment of generic HRQoL measured using the EQ-5D-5L questionnaire completed at baseline, 2 weeks, 8 weeks, 26 weeks and 52 weeks
7. Health impairment measured using the St George's Respiratory Questionnaire (SGRQ) at baseline, 2 weeks, 8 weeks, 26 weeks and 52 weeks
8. Patient preferences for treatment measured using a Treatment Satisfaction Questionnaire at 2, 8, 26, and 52 weeks
9. Adverse events over 52 weeks recorded as they occur by the PI or designee via interview with patients
10. Lung function over 52 weeks measured by spirometry testing at baseline, 2 weeks, 8 weeks, 26 weeks and 52 weeks
11. Adherence to HTS and carbocisteine over 52 weeks assessed via interview with patients at 2, 8, 26, and 52 weeks

Overall study start date
01/07/2017

Completion date
30/09/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 06/10/2022:
1. Diagnosis of BE on high resolution computed tomography (HRCT)/computed tomography (CT) scans
2. BE must be the primary respiratory diagnosis
3. One or more pulmonary exacerbations in the last year requiring antibiotics*
4. Production of daily sputum
5. Stable for 14 or more days before the first study visit with no changes to treatment

6. Willing to continue any other existing chronic medication throughout the study
7. 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

Previous inclusion criteria:
1. Diagnosis of BE on high resolution computed tomography (HRCT)/computed tomography (CT) scans
2. BE must be the primary respiratory diagnosis
3. Two or more pulmonary exacerbations in the last year requiring antibiotics*
4. Production of daily sputum
5. Stable for 14 or more days before the first study visit with no changes to treatment
6. Willing to continue any other existing chronic medication throughout the study
7. 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

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 288; UK Sample Size: 288

Total final enrolment
288

Key exclusion criteria
1. Age <18 years old
2. Patients with CF
3. Patients with COPD as a primary respiratory diagnosis
4. Current smokers, female ex-smokers with greater than 20 pack years and male ex-smokers with greater than 25 pack years
5. FEV1<30%
6. If being treated with long term macrolides, on treatment for less than 1 month before joining study
7. Patients on regular isotonic saline
8. Treatment with HTS, carbocisteine or any mucolytics within the past 30 days
9. Known intolerance or contraindication to HTS or carbocisteine.
10. Hypersensitivity to any of the active ingredients or the excipients of carbocisteine
11. Active peptic ulceration
12. Any heredity galactose intolerance, the Lapp-Lactase deficiency or glucose-galactose malabsorption.

13. Patients unable to swallow oral capsules.
14. Women who are pregnant or lactating
15. Participation in another Clinical Trial of an Investigational Product within 30 days

Date of first enrolment
27/06/2018

Date of final enrolment
30/09/2023

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Altnagelvin Area Hospital
Glenshane Road
Londonderry
United Kingdom
BT47 6SB

Study participating centre
Royal Free Hospital
Pond St
Hampstead
London
United Kingdom
NW3 2QG

Study participating centre
Royal Infirmary of Edinburgh
51 Little France Crescent
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EH16 4SA

Study participating centre
Freeman Hospital
Freeman Road
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Study participating centre

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Study participating centre
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Study participating centre
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HP21 8AL

Study participating centre
Blackpool Victoria Hospital
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Study participating centre
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Study participating centre
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B71 4HJ

Study participating centre
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/02tdmfk69

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 15/100/01

Results and Publications

Publication and dissemination plan
Manuscript preparation is in progress for publication of the study protocol in a peer-reviewed journal.

In accordance with the open access policies proposed by the NIHR the trialists aim to publish the following within approximately one year of the overall trial end date:
1. The trial protocol
2. The clinical findings of the trial
3. A paper describing the cost-effectiveness in the NHS setting in high quality peer-reviewed open access (via PubMed Central) journal.

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.

Intention to publish date
30/09/2025

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	19/12/2019	23/12/2019	Yes	No
HRA research summary			28/06/2023	No	No